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[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

11729.1 contg

11729-45.21.21.cons1

11729-45.21.21.cons2

11731.1contig

TCTTTTCTTTCGATTICCTTCAATTIGTCACGTTTGATTTTATGAAGTIGTTCAAGGGCTAACTGCTGTGTAT
TATAGCTTTCTCTGAGTTCCTTCAGCTGATTGTTAAATGAATCCATTTCTGAGAGCTTAGATGCAGTTCTTTT
TCAAGAGCATCTAATTGTTCTTTAAGTCTTTTGCATAATTCTTTCCTTTTTTCTGATGACTTTTTATGAAGTAAACT
GATCCCTGAATCAGGTGTTACTGAGCTGCATGTTTTTAATTCTTTCGTTTAATAGCTGCTTCTCAGGGACA
GATAGATAAGCTTATTTTGATATTCCTTAAGCTCTTGTGAAGTTGTTTGATTTCCATAATTCCAGGTCACA
TGTTTATCCAAAACTTTCTAGCTCAGTCTTTTGTGTTTGGTTTCGATTTGGACATCTTGTAGTCTGCCTGAGAT
CTGCTGATGXTTTCCAATTCACTGCTCCAGTTCCAGGTGAGACTTTXCTTTCTGGACCTCAGCCTGACAATGC
CTTCTTGTTGCTCCCT

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as ovarian cancer, are disclosed. Compositions may comprise one or more ovarian carcinoma proteins, immunogenic portions thereof, polynucleotides that encode such portions or antibodies or immune system cells specific for such proteins. Such compositions may be used, for example, for the prevention and treatment of diseases such as ovarian cancer. Methods are further provided for identifying tumor antigens that are secreted from ovarian carcinomas and/or other tumors. Polypeptides and polynucleotides as provided herein may further be used for the diagnosis and monitoring of ovarian cancer.

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COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF OVARIAN CANCER

Technical Field

The present invention relates generally to ovarian cancer therapy. The invention is more specifically related to polypeptides comprising at least a portion of an ovarian carcinoma protein, and to polynucleotides encoding such polypeptides, as well as antibodies and immune system cells that specifically recognize such polypeptides. Such polypeptides, polynucleotides, antibodies and cells may be used in vaccines and pharmaceutical compositions for treatment of ovarian cancer.

10 Background of the Invention

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Ovarian cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and therapy of this cancer, no vaccine or other universally successful method for prevention or treatment is currently available. Management of the disease currently relies on a combination of early diagnosis and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. However, the use of established markers often leads to a result that is difficult to interpret, and high mortality continues to be observed in many cancer patients.

Immunotherapies have the potential to substantially improve cancer treatment and survival. Such therapies may involve the generation or enhancement of an immune response to an ovarian carcinoma antigen. However, to date, relatively few ovarian carcinoma antigens are known and the generation of an immune response against such antigens has not been shown to be therapeutically beneficial.

Accordingly, there is a need in the art for improved methods for identifying ovarian tumor antigens and for using such antigens in the therapy of ovarian cancer. The present invention fulfills these needs and further provides other related advantages.

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SUMMARY OF THE INVENTION

Briefly stated, this invention provides compositions and methods for the therapy of cancer, such as ovarian cancer. In one aspect, the present invention provides polypeptides comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished. Within certain embodiments, the ovarian carcinoma protein comprises a sequence that is encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:456-457, 460-477 and 512-570 and complements of such polynucleotides.

The present invention further provides polynucleotides that encode a polypeptide as described above or a portion thereof, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

The present invention further provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596.

Within other aspects, the present invention provides pharmaceutical Pharmaceutical compositions may comprise a compositions and vaccines. physiologically acceptable carrier or excipient in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma proteinspecific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide. Vaccines may comprise a non-specific immune response enhancer in combination with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570 or (ii) a polynucleotide encoding such a polypeptide; (iii) an anti-idiotypic antibody that is specifically bound by an antibody that specifically binds to such a polypeptide; (iv) an antigen-presenting cell that expresses such a polypeptide and/or (v) a T cell that specifically reacts with such a polypeptide.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

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Within related aspects, pharmaceutical compositions comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, comprising a fusion protein or polynucleotide encoding a fusion protein in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for stimulating and/or expanding T cells, comprising contacting T cells with (a) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence set forth in SEQ ID Nos:394-455, 458-459, 478-511, and 571-596 or an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (b) a polynucleotide encoding such a polypeptide and/or (c) an antigen presenting cell that

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expresses such a polypeptide under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Such polypeptide, polynucleotide and/or antigen presenting cell(s) may be present within a pharmaceutical composition or vaccine, for use in stimulating and/or expanding T cells in a mammal.

Within other aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising administering to a patient T cells prepared as described above.

Within further aspects, the present invention provides methods for inhibiting the development of ovarian cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising an immunogenic portion of an ovarian carcinoma protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with ovarian carcinoma protein-specific antisera is not substantially diminished, wherein the ovarian carcinoma protein comprises an amino acid sequence encoded by a polynucleotide that comprises a sequence recited in any one of SEQ ID NO: 456-457, 460-477 and 512-570; (ii) a polynucleotide encoding such a polypeptide; or (iii) an antigen-presenting cell that expresses such a polypeptide; such that T cells proliferate; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of ovarian cancer in the patient. The proliferated cells may be cloned prior to administration to the patient.

The present invention also provides, within other aspects, methods for identifying secreted tumor antigens. Such methods comprise the steps of: (a) implanting tumor cells in an immunodeficient mammal; (b) obtaining serum from the immunodeficient mammal after a time sufficient to permit secretion of tumor antigens into the serum; (c) immunizing an immunocompetent mammal with the serum; (d) obtaining antiserum from the immunocompetent mammal; and (e) screening a tumor expression library with the antiserum, and therefrom identifying a secreted tumor antigen. A preferred method for identifying a secreted ovarian carcinoma antigen comprises the steps of: (a) implanting ovarian carcinoma cells in a SCID mouse; (b) obtaining serum from the SCID mouse after a time sufficient to permit secretion of

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ovarian carcinoma antigens into the serum; (c) immunizing an immunocompetent mouse with the serum; (d) obtaining antiserum from the immunocompetent mouse; and (e) screening an ovarian carcinoma expression library with the antiserum, and therefrom identifying a secreted ovarian carcinoma antigen.

The present invention also discloses antibody epitopes recognized by the O8E polyclonal anti-sera which epitopes are presented herein as SEQ ID NO: 394-415.

Further disclosed by the present invention are 10-mer and 9-mer peptides predicted to bind HLA-0201 which peptides are disclosed herein as SEQ ID NO:416-435 and SEQ ID NO:436-455, respectively.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

In another aspect of the present invention, the applicants have unexpectedly identified a series of novel repeating sequence elements in the 5' end of the gene encoding O772P. Therefore, the present invention provides O772P polypeptides having structures represented by X_n-Y, wherein X comprises a sequence having at least 50% identity, preferably at least 70% identity, and more preferably at least 90% identity with an O772P repeat sequence set forth in SEQ ID NO: 596. Y will typically comprise a sequence having at least 80% identity, preferably at least 90% identity and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 594. According to this embodiment, n will generally be an integer from 1 to 35, preferably an integer from 15 to 25, and X can be the same or different.

In one preferred embodiment, X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593 and Y comprises the sequence set forth in SEQ ID NO: 594.

In another preferred embodiment, an illustrative O772P polypeptide comprises the sequence set forth in SEQ ID NO: 595, containing 20 repeating sequence elements (i.e., X₂₀) wherein the X elements are arranged in the following order (moving from N-terminal to C-terminal in the O772P repeat region): SEQ ID NO: 574 - SEQ ID

NO: 575 - SEQ ID NO: 576 - SEQ ID NO: 577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO: 586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593.

According to another aspect of the present invention, an O772P polynucleotide is provided having the structure X_n -Y, wherein X comprises an O772P repeat sequence element selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567. Y will generally comprise a sequence having at least 80% identity, preferably at least 90% identity, and more preferably at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568. In this embodiment, n is typically an integer from 1 to 35, preferably from 15 to 25 and X can be the same or different.

In another embodiment, an illustrative O772P polynucleotide comprises the sequence set forth in SEQ ID NO: 569, containing 20 repeating sequence elements (i.e., X₂₀).

According to another aspect of the present invention, O772 polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.

According to another aspect of the present invention, O8E polypeptides are provided comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.

BRIEF DESCRIPTION OF THE SEQUENCE IDENTIFIERS AND DRAWINGS

SEQ ID NO:1-71 are ovarian carcinoma antigen polynucleotides shown 25 in Figures 1A-1S.

SEQ ID NO:72-74 are ovarian carcinoma antigen polynucleotides shown in Figures 2A-2C.

SEQ ID NO:75 is the ovarian carcinoma polynucleotide 3g (Figure 4).

SEQ ID NO:76 is the ovarian carcinoma polynucleotide 3f (Figure 5).

SEQ ID NO:77 is the ovarian carcinoma polynucleotide 6b (Figure 6).

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SEQ ID NO:78 is the ovarian carcinoma polynucleotide 8e (Figure 7A).

SEQ ID NO:79 is the ovarian carcinoma polynucleotide 8h (Figure 7B).

SEQ ID NO:80 is the ovarian carcinoma polynucleotide 12e (Figure 8).

SEQ ID NO:81 is the ovarian carcinoma polynucleotide 12h (Figure 9).

SEQ ID NO:82-310 are ovarian carcinoma antigen polynucleotides shown in Figures 15A-15EEE.

SEQ ID NO:311 is a full length sequence of ovarian carcinoma polynucleotide O772P.

SEQ ID NO:312 is the O772P amino acid sequence.

SEQ ID NO:313-384 are ovarian carcinoma antigen polynucleotides.

SEQ ID NO:385 represents the cDNA sequence of a form of the clone O772P, designated 21013.

SEQ ID NO:386 represents the cDNA sequence of a form of the clone O772P, designated 21003.

SEQ ID NO:387 represents the cDNA sequence of a form of the clone O772P, designated 21008.

SEQ ID NOs:388 is the amino acid sequence corresponding to SEQ ID NO:385.

SEQ ID NOs:389 is the amino acid sequence corresponding to SEQ ID NO:386.SEQ ID NOs:390 is the amino acid sequence corresponding to SEQ ID NO:387.

SEQ ID NO:391 is a full length sequence of ovarian carcinoma polynucleotide O8E.

SEQ ID NO:392-393 are protein sequences encoded by O8E.

SEQ ID NO:394-415 are peptide sequences corresponding to the OE8 antibody epitopes.

SEQ ID NO:416-435 are potential HLA-A2 10-mer binding peptides predicted using the full length open-reading frame from OE8.

SEQ ID NO:436-455 are potential HLA-A2 9-mer binding peptides predicted using the full length open-reading frame from OE8.

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SEQ ID NO:456 is a truncated nucleotide sequence of the full length Genbank sequence showing homology to O772P

SEQ ID NO:457 is the full length Genbank sequence showing significant homology to O772P

5 SEQ ID NO:458 is a protein encoding a truncated version of the full length Genbank sequence showing homology to O772P

SEQ ID NO:459 is the full length protein sequence from Genbank showing significant homology to the protein sequence for O772P

SEQ ID NO:460 encodes a unique N-terminal portion of O772P to contained in residues 1-70.

SEQ ID NO:461 contains unique sequence and encodes residues 1-313 of SEQ ID NO: 456.

SEQ ID NO:462 is the hypothetical sequence for clone O772P.

SEQ ID NO:463 is the cDNA sequence for clone FLJ14303.

SEQ ID NO:464 is a partial cDNA sequence for clone O772P.

SEQ ID NO:465 is a partial cDNA sequence for clone O772P.

SEQ ID NO:466 is a partial cDNA sequence for clone O772P.

SEQ ID NO:467 is a partial cDNA sequence for clone O772P.

SEQ ID NO:468 is a partial cDNA sequence for clone O772P.

SEQ ID NO:469 is a partial cDNA sequence for clone O772P.

SEQ ID NO:470 is a partial cDNA sequence for clone O772P.

SEQ ID NO:471 is a partial cDNA sequence for clone O772P.

SEQ ID NO:472 is a partial cDNA sequence for clone O772P.

SEQ ID NO:473 is a partial cDNA sequence for clone O772P.

SEQ ID NO:474 is a partial cDNA sequence for clone O772P.

SEQ ID NO:475 is a partial cDNA sequence for clone O772P.

SEQ ID NO:476 is a partial cDNA sequence for clone O772P.

SEQ ID NO:477 represents the novel 5'-end of the ovarian tumor antigen

O772P.

SEQ ID NO:478 is the amino acid sequence encoded by SEQ ID NO:462.

SEQ ID NO:479 is the amino acid sequence encoded by SEQ ID NO:463.

SEQ ID NO:480 is a partial amino acid sequence encoded by SEQ ID NO:472.

SEQ ID NO:481 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:471.

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SEQ ID NO:482 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:471.

SEQ ID NO:483 is a partial amino acid sequence encoded by SEQ ID 10 NO:467.

SEQ ID NO:484 is a partial amino acid sequence encoded by a possible open reading frame of SEQ ID NO:466.

SEQ ID NO:485 is a partial amino acid sequence encoded by a second possible open reading frame of SEQ ID NO:466.

SEQ ID NO:486 is a partial amino acid sequence encoded by SEQ ID NO:465.

SEQ ID NO:487 is a partial amino acid sequence encoded by SEQ ID NO:464.

SEQ ID NO:488 represents the extracellular, transmembrane and 20 cytoplasmic regions of O772P.

SEQ ID NO:489 represents the predicted extracellular domain of O772P.

SEQ ID NO:490 represents the amino acid sequence of peptide #2 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:491 represents the amino acid sequence of peptide #6 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:492 represents the amino acid sequence of peptide #7 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:493 represents the amino acid sequence of peptide #8 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:494 represents the amino acid sequence of peptide #9 which corresponds to an O772P specific antibody epitope.

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SEQ ID NO:495 represents the amino acid sequence of peptide #11 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:496 represents the amino acid sequence of peptide #13 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:497 represents the amino acid sequence of peptide #22 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:498 represents the amino acid sequence of peptide #24 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:499 represents the amino acid sequence of peptide #27 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:500 represents the amino acid sequence of peptide #40 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:501 represents the amino acid sequence of peptide #41 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:502 represents the amino acid sequence of peptide #47 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:503 represents the amino acid sequence of peptide #50 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:504 represents the amino acid sequence of peptide #51 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:505 represents the amino acid sequence of peptide #52 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:506 represents the amino acid sequence of peptide #53 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:507 represents the amino acid sequence of peptide #58 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:508 represents the amino acid sequence of peptide #59 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:509 represents the amino acid sequence of peptide #60 which corresponds to an O772P specific antibody epitope.

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SEQ ID NO:510 represents the amino acid sequence of peptide #61 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:511 represents the amino acid sequence of peptide #71 which corresponds to an O772P specific antibody epitope.

SEQ ID NO:512 (O772P repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:513 (O772P repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:514 (O772P repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:515 (O772P repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:516 (O772P repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:517 (HB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:518 (HB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:519 (HB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:520 (HB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:521 (HB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:522 (HB repeat6 5'-end) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:523 (1043400.1 repeat1) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:524 (1043400.1 repeat2) represents an example of a cDNA

30 sequence corresponding to repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:525 (1043400.1 repeat3) represents an example of a cDNA sequence corresponding to repeat number 10/11 from the 5' variable region of O772P. SEQ ID NO:526 (1043400.1 repeat4) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P. SEQ ID NO:527 (1043400.1 repeat5) represents an example of a cDNA 5 sequence corresponding to repeat number 14 from the 5' variable region of O772P. SEQ ID NO:528 (1043400.1 repeat6) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P. SEO ID NO:529 (1043400.3 repeat1) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P. 10 SEO ID NO:530 (1043400.3 repeat2) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P. SEQ ID NO:531 (1043400.5 repeat1) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P. SEQ ID NO:532 (1043400.5 repeat2) represents an example of a cDNA 15 sequence corresponding to repeat number 9 from the 5' variable region of O772P, in addition containing intron sequence. SEO ID NO:533 (1043400.5 repeat2) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P. SEQ ID NO:534 (1043400.8 repeat1) represents an example of a cDNA 20 sequence corresponding to repeat number 17 from the 5' variable region of O772P. SEO ID NO:535 (1043400.8 repeat2) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P. SEO ID NO:536 (1043400.8 repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P. 25 SEQ ID NO:537 (1043400.9 repeat1) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P. SEQ ID NO:538 (1043400.9 repeat2) represents an example of a cDNA sequence corresponding to repeat number 5 from the 5' variable region of O772P. SEQ ID NO:539 (1043400.9 repeat3) represents an example of a cDNA 30

sequence corresponding to repeat number 7 from the 5' variable region of O772P.

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SEQ ID NO:540 (1043400.9 repeat4) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P. SEQ ID NO:541 (1043400.11 repeat1) represents an example of a cDNA sequence corresponding to repeat number 1 from the 5' variable region of O772P. SEQ ID NO:542 (1043400.11 repeat2) represents an example of a cDNA sequence corresponding to repeat number 2 from the 5' variable region of O772P. SEQ ID NO:543 (1043400.11 repeat3) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P. SEQ ID NO:544 (1043400.11 repeat4) represents an example of a cDNA 10 sequence corresponding to repeat number 11 from the 5' variable region of O772P. SEQ ID NO:545 (1043400.11 repeat5) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P. SEQ ID NO:546 (1043400.12 repeat1) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P. SEQ ID NO:547 (PB repeatA) represents an example of a cDNA sequence corresponding to repeat number 1 from the 5' variable region of O772P. SEQ ID NO:548 (PB repeatB) represents an example of a cDNA sequence corresponding to repeat number 2 from the 5' variable region of O772P. SEQ ID NO:549 (PB repeatE) represents an example of a cDNA sequence corresponding to repeat number 3 from the 5' variable region of O772P. SEQ ID NO:550 (PB repeatG) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P. SEQ ID NO:551 (PB repeatC) represents an example of a cDNA sequence corresponding to repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:552 (PB repeatH) represents an example of a cDNA sequence corresponding to repeat number 6 from the 5' variable region of O772P. SEQ ID NO:553 (PB repeatJ) represents an example of a cDNA sequence corresponding to repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:554 (PB repeatK) represents an example of a cDNA sequence corresponding to repeat number 8 from the 5' variable region of O772P.

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SEQ ID NO:555 (PB repeatD) represents an example of a cDNA sequence corresponding to repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:556 (PB repeatl) represents an example of a cDNA sequence corresponding to repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:557 (PB repeatM) represents an example of a cDNA sequence corresponding to repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:558 (PB repeat9) represents an example of a cDNA sequence corresponding to repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:559 (PB repeat8.5) represents an example of a cDNA sequence corresponding to repeat number 13 from the 5' variable region of O772P.

SEQ ID NO:560 (PB repeat8) represents an example of a cDNA sequence corresponding to repeat number 14 from the 5' variable region of O772P.

SEQ ID NO:561 (PB repeat7) represents an example of a cDNA sequence corresponding to repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:562 (PB repeat6) represents an example of a cDNA sequence corresponding to repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:563 (PB repeat5) represents an example of a cDNA sequence corresponding to repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:564 (PB repeat4) represents an example of a cDNA sequence corresponding to repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:565 (PB repeat3) represents an example of a cDNA sequence corresponding to repeat number 19 from the 5' variable region of O772P.

SEQ ID NO:566 (PB repeat2) represents an example of a cDNA sequence corresponding to repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:567 (PB repeat1) represents an example of a cDNA sequence corresponding to repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:568 represents the cDNA sequence form the 3' constant region.

SEQ ID NO:569 represents a cDNA sequence containing the consensus sequences of the 21 repeats, the 3' constant region and the 3' untranslated region.

SEQ ID NO:570 represents the cDNA sequence of the consensus repeat sequence.

SEQ ID NO:571 represents the consensus amino acid sequence of one potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:572 represents the consensus amino acid sequence of a second potential open reading frame of repeat number 1 from the 5' variable region of O772P.

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SEQ ID NO:573 represents the consensus amino acid sequence of a third potential open reading frame of repeat number 1 from the 5' variable region of O772P.

SEQ ID NO:574 represents the consensus amino acid sequence of repeat number 2 from the 5' variable region of O772P.

SEQ ID NO:575 represents the consensus amino acid sequence of repeat number 3 from the 5' variable region of O772P.

SEQ ID NO:576 represents the consensus amino acid sequence of repeat number 4 from the 5' variable region of O772P.

SEQ ID NO:577 represents the consensus amino acid sequence of repeat number 5 from the 5' variable region of O772P.

SEQ ID NO:578 represents the consensus amino acid sequence of repeat number 6 from the 5' variable region of O772P.

SEQ ID NO:579 represents the consensus amino acid sequence of repeat number 7 from the 5' variable region of O772P.

SEQ ID NO:580 represents the consensus amino acid sequence of repeat number 8 from the 5' variable region of O772P.

SEQ ID NO:581 represents the consensus amino acid sequence of repeat number 9 from the 5' variable region of O772P.

SEQ ID NO:582 represents the consensus amino acid sequence of repeat number 10 from the 5' variable region of O772P.

SEQ ID NO:583 represents the consensus amino acid sequence of repeat number 11 from the 5' variable region of O772P.

SEQ ID NO:584 represents the consensus amino acid sequence of repeat number 12 from the 5' variable region of O772P.

SEQ ID NO:585 represents the consensus amino acid sequence of repeat number 13 from the 5' variable region of O772P.

SEQ ID NO:586 represents the consensus amino acid sequence of repeat number 14 from the 5' variable region of O772P.

SEQ ID NO:587 represents the consensus amino acid sequence of repeat number 15 from the 5' variable region of O772P.

SEQ ID NO:588 represents the consensus amino acid sequence of repeat number 16 from the 5' variable region of O772P.

SEQ ID NO:589 represents the consensus amino acid sequence of repeat number 17 from the 5' variable region of O772P.

SEQ ID NO:590 represents the consensus amino acid sequence of repeat number 18 from the 5' variable region of O772P.

SEQ ID NO:591 represents the consensus amino acid sequence of repeat number 19 from the 5' variable region of O772P.

15 SEQ ID NO:592 represents the consensus amino acid sequence of repeat number 20 from the 5' variable region of O772P.

SEQ ID NO:593 represents the consensus amino acid sequence of repeat number 21 from the 5' variable region of O772P.

SEQ ID NO:594 represents the amino acid sequence of the 3' constant 20 region.

SEQ ID NO:595 represents an amino acid sequence containing the consensus sequences of the 21 repeats and the 3' constant region.

SEQ ID NO:596 represents the amino acid sequence of the consensus repeat sequence.

25 Figures 1A-1S (SEQ ID NO:1-71) depict partial sequences of polynucleotides encoding representative secreted ovarian carcinoma antigens.

Figure 2A-2C depict full insert sequences for three of the clones of Figure 1. Figure 2A shows the sequence designated O7E (11731; SEQ ID NO:72), Figure 2B shows the sequence designated O9E (11785; SEQ ID NO:73) and Figure 2C shows the sequence designated O8E (13695; SEQ ID NO:74).

Figure 3 presents results of microarray expression analysis of the ovarian carcinoma sequence designated O8E.

Figure 4 presents a partial sequence of a polynucleotide (designated 3g; SEQ ID NO:75) encoding an ovarian carcinoma sequence that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX and osteonectin.

Figure 5 presents the ovarian carcinoma polynucleotide designated 3f (SEQ ID NO:76).

Figure 6 presents the ovarian carcinoma polynucleotide designated 6b (SEQ ID NO:77).

Figures 7A and 7B present the ovarian carcinoma polynucleotides designated 8e (SEQ ID NO:78) and 8h (SEQ ID NO:79).

Figure 8 presents the ovarian carcinoma polynucleotide designated 12c (SEQ ID NO:80).

Figure 9 presents the ovarian carcinoma polynucleotide designated 12h (SEQ ID NO:81).

Figure 10 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 3f.

Figure 11 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 6b.

Figure 12 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 8e.

Figure 13 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12c.

Figure 14 depicts results of microarray expression analysis of the ovarian carcinoma sequence designated 12h.

Figures 15A-15EEE depict partial sequences of additional polynucleotides encoding representative secreted ovarian carcinoma antigens (SEQ ID NO:82-310).

Figure 16 is a diagram illustrating the location of various partial O8E sequences within the full length sequence.

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Figure 17 is a graph illustrating the results of epitope mapping studies on O8E protein.

Figure 18 is graph of a fluorescence activated cell sorting (FACS) analysis of O8E cell surface expression.

Figure 19 is graph of a FACS analysis of O8E cell surface expression.

Figure 20 shows FACS analysis results for O8E transfected HEK293 cells demonstrating cell surface expression of O8E.

Figure 21 shows FACS analysis results for SKBR3 breast tumor cells demonstrating cell surface expression of O8E.

Figure 22 shows 08E expression in HEK 293 cells. The cells were probed with anti-08E rabbit polyclonal antisera #2333L.

Figure 23 shows the ELISA analysis of anti-08E rabbit sera.

Figure 24 shows the ELISA analysis of affinity purified rabbit anti-08E polyclonal antibody.

Figure 25 is a graph determining antibody internalization of anti-O8E mAb showing that mAbs against amino acids 61-80 induces ligand internalization.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy of cancer, such as ovarian cancer. The compositions described herein may include immunogenic polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies that bind to a polypeptide, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells).

Polypeptides of the present invention generally comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof. Certain ovarian carcinoma proteins have been identified using an immunoassay technique, and are referred to herein as ovarian carcinoma antigens. An "ovarian carcinoma antigen" is a protein that is expressed by ovarian tumor cells (preferably human cells) at a level that is at least two fold higher than the level in normal ovarian cells. Certain ovarian carcinoma antigens react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera generated against serum from an immunodeficient animal

implanted with a human ovarian tumor. Such ovarian carcinoma antigens are shed or secreted from an ovarian tumor into the sera of the immunodeficient animal. Accordingly, certain ovarian carcinoma antigens provided herein are secreted antigens. Certain nucleic acid sequences of the subject invention generally comprise a DNA or 5 RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence.

The present invention further provides ovarian carcinoma sequences that are identified using techniques to evaluate altered expression within an ovarian tumor. Such sequences may be polynucleotide or protein sequences. Ovarian carcinoma 10 sequences are generally expressed in an ovarian tumor at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal ovarian tissue, as determined using a representative assay provided herein. Certain partial ovarian carcinoma polynucleotide sequences are presented herein. Proteins encoded by genes comprising such polynucleotide sequences (or complements thereof) are also considered ovarian carcinoma proteins.

Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to at least a portion of an ovarian carcinoma polypeptide as described herein. T cells that may be employed within the compositions provided herein are generally T cells (e.g., CD4⁺ and/or CD8⁺) that are specific for such a polypeptide. Certain methods described herein further employ antigen-presenting cells (such as dendritic cells or macrophages) that express an ovarian carcinoma polypeptide as provided herein.

Ovarian Carcinoma Polynucleotides

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Any polynucleotide that encodes an ovarian carcinoma protein or a 25 portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides, and more preferably at least 45 consecutive nucleotides, that encode a portion of an ovarian carcinoma protein. More preferably, a polynucleotide encodes an immunogenic portion of an ovarian carcinoma protein, such as an ovarian carcinoma antigen. Polynucleotides complementary to any

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such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes an ovarian carcinoma protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native ovarian carcinoma protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native ovarian carcinoma protein or a portion thereof.

The percent identity for two polynucleotide or polypeptide sequences may be readily determined by comparing sequences using computer algorithms well known to those of ordinary skill in the art, such as Megalign, using default parameters. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, or 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Optimal alignment of sequences for comparison may be conducted, for example, using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. Preferably, the percentage of sequence identity is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the window may comprise additions or deletions (i.e., gaps) of 20 % or less, usually 5 to 15 %, or 10 to 12%, relative to the reference sequence (which does not contain additions or deletions). The percent identity may be calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native ovarian carcinoma protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

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Polynucleotides may be prepared using any of a variety of techniques. For example, an ovarian carcinoma polynucleotide may be identified, as described in more detail below, by screening a late passage ovarian tumor expression library with antisera generated against sera of immunocompetent mice after injection of such mice with sera from SCID mice implanted with late passage ovarian tumors. Ovarian carcinoma polynucleotides may also be identified using any of a variety of techniques designed to evaluate differential gene expression. Alternatively, polynucleotides may

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be amplified from cDNA prepared from ovarian tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., an ovarian carcinoma cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is sizeselected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ³²P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using 20 a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

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Certain nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma antigens are provided in Figures 1A-1S (SEQ ID NO:1 to 71) and Figures 15A to 15EEE (SEQ ID NO:82 to 310). The sequences provided in Figures 1A-1S appear to be novel. For sequences in Figures 15A-15EEE, database searches revealed matches having substantial identity. These polynucleotides were isolated by serological screening of an ovarian tumor cDNA expression library, using a technique designed to identify secreted tumor antigens. Briefly, a late passage ovarian tumor expression library was prepared from a SCID-derived human ovarian tumor (OV9334) in the vector λ-screen (Novagen). The sera used for screening were obtained by

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injecting immunocompetent mice with sera from SCID mice implanted with one late passage ovarian tumors. This technique permits the identification of cDNA molecules that encode immunogenic portions of secreted tumor antigens.

The polynucleotides recited herein, as well as full length polynucleotides comprising such sequences, other portions of such full length polynucleotides, and sequences complementary to all or a portion of such full length molecules, are specifically encompassed by the present invention. It will be apparent to those of ordinary skill in the art that this technique can also be applied to the identification of antigens that are secreted from other types of tumors.

Other nucleic acid sequences of cDNA molecules encoding portions of ovarian carcinoma proteins are provided in Figures 4-9 (SEQ ID NO:75-81), as well as SEQ ID NO:313-384. These sequences were identified by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in an ovarian tumor than in normal ovarian tissue, as determined using a representative assay provided herein). Such screens were performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). SEQ ID NO:311 and 391 provide full length sequences incorporating certain of these nucleic acid sequences.

Any of a variety of well known techniques may be used to evaluate tumor-associated expression of a cDNA. For example, hybridization techniques using labeled polynucleotide probes may be employed. Alternatively, or in addition, amplification techniques such as real-time PCR may be used (see Gibson et al., Genome Research 6:995-1001, 1996; Heid et al., Genome Research 6:986-994, 1996). Real-time PCR is a technique that evaluates the level of PCR product accumulation during amplification. This technique permits quantitative evaluation of mRNA levels in multiple samples. Briefly, mRNA is extracted from tumor and normal tissue and cDNA is prepared using standard techniques. Real-time PCR may be performed, for example, using a Perkin Elmer/Applied Biosystems (Foster City, CA) 7700 Prism instrument. Matching primers and fluorescent probes may be designed for genes of interest using, for example, the primer express program provided by Perkin Elmer/Applied Biosystems

(Foster City, CA). Optimal concentrations of primers and probes may be initially determined by those of ordinary skill in the art, and control (e.g., β-actin) primers and probes may be obtained commercially from, for example, Perkin Elmer/Applied Biosystems (Foster City, CA). To quantitate the amount of specific RNA in a sample, a standard curve is generated alongside using a plasmid containing the gene of interest. Standard curves may be generated using the Ct values determined in the real-time PCR, which are related to the initial cDNA concentration used in the assay. Standard dilutions ranging from 10-10⁶ copies of the gene of interest are generally sufficient. In addition, a standard curve is generated for the control sequence. This permits standardization of initial RNA content of a tissue sample to the amount of control for comparison purposes.

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Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding an ovarian carcinoma antigen, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo.

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells or tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of an ovarian carcinoma protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches,

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Futura Publishing Co. (Mt. Kisco, NY; 1994). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

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Any polynucleotide may be further modified to increase stability in vivo. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also

be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

Ovarian Carcinoma Polypeptides

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Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of an ovarian carcinoma protein or a variant thereof, as described herein. As noted above, certain ovarian carcinoma proteins are ovarian carcinoma antigens that are expressed by ovarian tumor cells and react detectably within an immunoassay (such as an ELISA) with antisera generated against serum from an immunodeficient animal implanted with an ovarian tumor. Other ovarian carcinoma proteins are encoded by ovarian carcinoma polynucleotides recited herein. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of an antigen that is recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of an ovarian carcinoma protein or a variant thereof. Preferred immunogenic portions are encoded by cDNA molecules isolated as described herein. Further immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with ovarian carcinoma protein-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "ovarian carcinoma protein-

specific" if they specifically bind to an ovarian carcinoma protein (i.e., they react with the ovarian carcinoma protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera, antibodies and T cells may be prepared as described herein, and using well known techniques. An immunogenic portion of a native ovarian carcinoma protein is a portion that reacts with such antisera, antibodies and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length protein. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ¹²⁵I-labeled Protein A.

As noted above, a composition may comprise a variant of a native ovarian carcinoma protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native ovarian carcinoma protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with ovarian carcinoma protein-specific antisera may be enhanced or unchanged, relative to the native ovarian carcinoma protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native ovarian carcinoma protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with ovarian carcinoma protein-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity to the native polypeptide. Preferably, a variant contains conservative substitutions. "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

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Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells

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include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc. (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises one polypeptide as described herein and a known tumor antigen, such as an ovarian carcinoma protein or a variant of such a protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, 30 including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused

protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, As and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., 20 Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

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The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

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Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen present cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

WO 02/06317 PCT/US01/22635

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In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

Binding Agents

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The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to an ovarian carcinoma protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to an ovarian carcinoma protein if it reacts at a detectable level (within, for example, an ELISA) with an ovarian carcinoma protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a "complex" is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10³ L/mol. The binding constant maybe determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as ovarian cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a ovarian carcinoma antigen will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological

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samples (e.g., blood, sera, leukophoresis, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the

desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

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Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include

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methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of

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derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Also provided herein are anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein. Such antibodies may be raised against an antibody, or antigen-binding fragment thereof, that specifically binds to an

immunogenic portion of an ovarian carcinoma protein, using well known techniques. Anti-idiotypic antibodies that mimic an immunogenic portion of an ovarian carcinoma protein are those antibodies that bind to an antibody, or antigen-binding fragment thereof, that specifically binds to an immunogenic portion of an ovarian carcinoma protein, as described herein.

T Cells

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Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for an ovarian carcinoma protein. Such cells may generally be prepared in vitro or ex vivo, using standard procedures. For example, T cells may be present within (or isolated from) bone marrow, peripheral blood or a fraction of bone marrow or peripheral blood of a mammal, such as a patient, using a commercially available cell separation system, such as the CEPRATETM system, available from CellPro Inc., Bothell WA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human animals, cell lines or cultures.

T cells may be stimulated with an ovarian carcinoma polypeptide, polynucleotide encoding an ovarian carcinoma polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, an ovarian carcinoma polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for an ovarian carcinoma polypeptide if the T cells kill target cells coated with an ovarian carcinoma polypeptide or expressing a gene encoding such a polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be

accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with an ovarian carcinoma polypeptide (200 ng/ml - 100 μg/ml, preferably 100 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells and/or contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998). T cells that have been activated in response to an ovarian carcinoma polypeptide, polynucleotide or ovarian carcinoma polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Ovarian carcinoma polypeptide-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient or a related or

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to an ovarian carcinoma polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to an ovarian carcinoma polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize an ovarian carcinoma polypeptide. Alternatively, one or more T cells that proliferate in the presence of an ovarian carcinoma polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution. Following expansion, the cells may be administered back to the patient as described, for example, by Chang et al., *Crit. Rev. Oncol. Hematol. 22*:213, 1996.

unrelated donor and are administered to the patient following stimulation and

Pharmaceutical Compositions and Vaccines

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expansion.

Within certain aspects, polypeptides, polynucleotides, binding agents 30 and/or immune system cells as described herein may be incorporated into

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pharmaceutical compositions or vaccines. Pharmaceutical compositions comprise one or more such compounds or cells and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds or cells and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., PNAS 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0.345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., PNAS 91:215-219, 1994; Kass-Eisler et al., PNAS 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

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Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune

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responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI), Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ), alum, biodegradable microspheres, monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). Also preferred is AS-2 (SmithKline Beecham). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO

96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

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Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects per se and/or to be immunologically compatible with the receiver (i.e., matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to

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be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (see Timmerman and Levy, Ann. Rev. Med. 50:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate in situ, with marked cytoplasmic processes (dendrites) visible in vitro) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells in vivo or ex vivo, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (see Zitvogel et al., Nature Med. 4:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a ovarian carcinoma antigen (or portion or other variant thereof) such that the antigen, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

Cancer Therapy

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In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as ovarian cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Within certain preferred embodiments, a patient is afflicted with ovarian cancer. Such cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

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Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immuno response-modifying agents (such as tumor vaccines, bacterial adjuvants and/or cytokines).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (such as CD8⁺ cytotoxic T lymphocytes and CD4⁺ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigenpresenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system.

Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term in vivo. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into stem cells taken from a patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

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Routes and frequency of administration, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration), orally or in the bed of a resected tumor. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level.. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical

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outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to an ovarian carcinoma antigen generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

Screens for Identifying Secreted Ovarian Carcinoma Antigens

The present invention provides methods for identifying secreted tumor antigens. Within such methods, tumors are implanted into immunodeficient animals such as SCID mice and maintained for a time sufficient to permit secretion of tumor antigens into serum. In general, tumors may be implanted subcutaneously or within the gonadal fat pad of an immunodeficient animal and maintained for 1-9 months, preferably 1-4 months. Implantation may generally be performed as described in WO 97/18300. The serum containing secreted antigens is then used to prepare antisera in immunocompetent mice, using standard techniques and as described herein. Briefly, 50-100 µL of sera (pooled from three sets of immunodeficient mice, each set bearing a different SCID-derived human ovarian tumor) may be mixed 1:1 (vol:vol) with an appropriate adjuvant, such as RIBI-MPL or MPL + TDM (Sigma Chemical Co., St. Louis, MO) and injected intraperitoneally into syngeneic immunocompetent animals at monthly intervals for a total of 5 months. Antisera from animals immunized in such a manner may be obtained by drawing blood after the third, fourth and fifth immunizations. The resulting antiserum is generally pre-cleared of E. coli and phage antigens and used (generally following dilution, such as 1:200) in a serological expression screen.

The library is typically an expression library containing cDNAs from one or more tumors of the type that was implanted into SCID mice. This expression library may be prepared in any suitable vector, such as λ -screen (Novagen). cDNAs that encode a polypeptide that reacts with the antiserum may be identified using standard techniques, and sequenced. Such cDNA molecules may be further characterized to

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evaluate expression in tumor and normal tissue, and to evaluate antigen secretion in patients.

The methods provided herein have advantages over other methods for tumor antigen discovery. In particular, all antigens identified by such methods should be secreted or released through necrosis of the tumor cells. Such antigens may be present on the surface of tumor cells for an amount of time sufficient to permit targeting and killing by the immune system, following vaccination.

Methods for Detecting Cancer

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In general, a cancer may be detected in a patient based on the presence of one or more ovarian carcinoma proteins and/or polynucleotides encoding such proteins in a biological sample (such as blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as ovarian cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of protein that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, an ovarian carcinoma-associated sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding

agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length ovarian carcinoma proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 µg, and preferably about 100 ng to about 1 µg, is sufficient to immobilize an adequate amount of binding agent.

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Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

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More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (i.e., incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with ovarian cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over

a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20TM. The second 5 antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibodypolypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of 10 binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups 15 and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as ovarian cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, 30 p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity)

that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

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In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use ovarian carcinoma polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such ovarian carcinoma protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with an ovarian carcinoma protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with an ovarian carcinoma protein, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with an ovarian carcinoma protein (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of ovarian carcinoma protein to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8⁺ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding an ovarian carcinoma protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of an ovarian carcinoma protein cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the ovarian carcinoma protein. The amplified cDNA is then separated and detected using techniques well

known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding an ovarian carcinoma protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

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To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding an ovarian carcinoma protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence provided herein. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample such as a biopsy tissue and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

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In another embodiment, ovarian carcinoma proteins and polynucleotides encoding such proteins may be used as markers for monitoring the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple ovarian carcinoma protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

Diagnostic Kits

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to an ovarian carcinoma protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain

a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding an ovarian carcinoma protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding an ovarian carcinoma protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding an ovarian carcinoma protein.

The following Examples are offered by way of illustration and not by way of limitation.

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EXAMPLES

EXAMPLE 1

IDENTIFICATION OF REPRESENTATIVE OVARIAN CARCINOMA PROTEIN CDNAS

This Example illustrates the identification of cDNA molecules encoding ovarian carcinoma proteins.

Anti-SCID mouse sera (generated against sera from SCID mice carrying late passage ovarian carcinoma) was pre-cleared of E. coli and phage antigens and used at a 1:200 dilution in a serological expression screen. The library screened was made from a SCID-derived human ovarian tumor (OV9334) using a directional RH oligo(dT) priming cDNA library construction kit and the λScreen vector (Novagen). A bacteriophage lambda screen was employed. Approximately 400,000 pfu of the amplified OV9334 library were screened.

196 positive clones were isolated. Certain sequences that appear to be novel are provided in Figures 1A-1S and SEQ ID NO:1 to 71. Three complete insert sequences are shown in Figures 2A-2C (SEQ ID NO:72 to 74). Other clones having known sequences are presented in Figures 15A-15EEE (SEQ ID NO:82 to 310). Database searches identified the following sequences that were substantially identical to the sequences presented in Figures 15A-15EEE.

These clones were further characterized using microarray technology to determine mRNA expression levels in a variety of tumor and normal tissues. Such analyses were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions. PCR amplification products were arrayed on slides, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes and the slides were scanned to measure fluorescence intensity. Data was analyzed using Synteni's provided GEMtools software. The results for one clone (13695, also referred to as O8E) are shown in Figure 3.

EXAMPLE 2

IDENTIFICATION OF OVARIAN CARCINOMA CDNAs USING MICROARRAY TECHNOLOGY

This Example illustrates the identification of ovarian carcinoma polynucleotides by PCR subtraction and microarray analysis. Microarrays of cDNAs were analyzed for ovarian tumor-specific expression using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997).

A PCR subtraction was performed using a tester comprising cDNA of four ovarian tumors (three of which were metastatic tumors) and a driver of cDNA form five normal tissues (adrenal gland, lung, pancreas, spleen and brain). cDNA fragments recovered from this subtraction were subjected to DNA microarray analysis where the fragments were PCR amplified, adhered to chips and hybridized with fluorescently labeled probes derived from mRNAs of human ovarian tumors and a variety of normal human tissues. In this analysis, the slides were scanned and the fluorescence intensity was measured, and the data were analyzed using Synteni's GEMtools software. In general, sequences showing at least a 5-fold increase in expression in tumor cells (relative to normal cells) were considered ovarian tumor antigens. The fluorescent results were analyzed and clones that displayed increased expression in ovarian tumors were further characterized by DNA sequencing and database searches to determine the novelty of the sequences.

Using such assays, an ovarian tumor antigen was identified that is a splice fusion between the human T-cell leukemia virus type I oncoprotein TAX (see Jin et al., Cell 93:81-91, 1998) and an extracellular matrix protein called osteonectin. A splice junction sequence exists at the fusion point. The sequence of this clone is presented in Figure 4 and SEQ ID NO:75. Osteonectin, unspliced and unaltered, was also identified from such assays independently.

Further clones identified by this method are referred to herein as 3f, 6b, 8e, 8h, 12c and 12h. Sequences of these clones are shown in Figures 5 to 9 and SEQ ID NO:76 to 81. Microarray analyses were performed as described above, and are presented in Figures 10 to 14. A full length sequence encompassing clones 3f, 6b, 8e

and 12h was obtained by screening an ovarian tumor (SCID-derived) cDNA library. This 2996 base pair sequence (designated O772P) is presented in SEQ ID NO:311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO:312. PSORT analysis indicates a Type 1a transmembrane protein localized to the plasma membrane.

In addition to certain of the sequences described above, this screen identified the following sequences which are described in detail in Table 1:

Table 1

Sequence	Comments
OV4vG11 (SEQ ID NO:313)	human clone 1119D9 on chromosome 20p12
OV4vB11 (SEQ ID NO:314)	human UWGC:y14c094 from chromosome 6p21
OV4vD9 (SEQ ID NO:315)	human clone 1049G16 chromosome 20q12-13.2
OV4vD5 (SEQ ID NO:316)	human KIAA0014 gene
OV4vC2 (SEQ ID NO:317)	human KIAA0084 gene
OV4vF3 (SEQ ID NO:318)	human chromosome 19 cosmid R31167
OV4VC1 (SEQ ID NO:319)	novel
OV4vH3 (SEQ ID NO:320)	novel
OV4vD2 (SEQ ID NO:321)	novel
O815P (SEQ ID NO:322)	novel
OV4vC12 (SEQ ID NO:323)	novel
OV4vA4 (SEQ ID NO:324)	novel
OV4vA3 (SEQ ID NO:325)	novel
OV4v2A5 (SEQ ID NO:326)	novel
O819P (SEQ ID NO:327)	novel
O818P (SEQ ID NO:328)	novel
O817P (SEQ ID NO:329)	novel
O816P (SEQ ID NO:330)	novel
Ov4vC5 (SEQ ID NO:331)	novel
21721 (SEQ ID NO:332)	human lumican
21719 (SEQ ID NO:333)	human retinoic acid-binding protein II
21717 (SEQ ID NO:334)	human26S proteasome ATPase subunit
21654 (SEQ ID NO:335)	human copine I
21627 (SEQ ID NO:336)	human neuron specific gamma-2 enolase

Sequence		
	Comments	
21623 (SEQ ID NO:337)	human geranylgeranyl transferase II	
21621 (SEQ ID NO:338)	human cyclin-dependent protein kinase	
21616 (SEQ ID NO:339)	human prepro-megakaryocyte potentiating factor	
21612 (SEQ ID NO:340)	human UPH1	
21558 (SEQ ID NO:341)	human RalGDS-like 2 (RGL2)	
21555 (SEQ ID NO:342)	human autoantigen P542	
21548 (SEQ ID NO:343)	human actin-related protein (ARP2)	
21462 (SEQ ID NO:344)	human huntingtin interacting protein	
21441 (SEQ ID NO:345)	human 90K product (tumor associated antigen)	
21439 (SEQ ID NO:346)	human guanine nucleotide regulator protein (tim1)	
21438 (SEQ ID NO:347)	human Ku autoimmune (p70/p80) antigen	
21237 (SEQ ID NO:348)	human S-laminin	
21436 (SEQ ID NO:349)	human ribophorin I	
21435 (SEQ ID NO:350)	human cytoplasmic chaperonin hTRiC5	
21425 (SEQ ID NO:351)	humanEMX2	
21423 (SEQ ID NO:352)	human p87/p89 gene	
21419 (SEQ ID NO:353)	human HPBRII-7	
21252 (SEQ ID NO:354)	human T1-227H	
21251 (SEQ ID NO:355)	human cullin I	
21247 (SEQ ID NO:356)	kunitz type protease inhibitor (KOP)	
21244-1 (SEQ ID NO:357)	human protein tyrosine phosphatase receptor F (PTPRF)	
21718 (SEQ ID NO:358)	human LTR repeat	
OV2-90 (SEQ ID NO:359)	novel	
Human zinc finger (SEQ ID NO:360)		
Human polyA binding protein (SEQ ID NO:361)		
Human pleitrophin (SEQ ID NO:362)		
Human PAC clone 278C19 (SEQ ID NO:363)		
Human LLRep3 (SEQ ID NO:364)		
Human Kunitz type protease inhib (SEQ ID NO:365)		
Human KIAA0106 gene (SEQ ID NO:366)		
Human keratin (SEQ ID NO:367)		
Human HIV-1TAR (SEQ ID NO:368)		
Human glia derived nexin (SEQ ID NO:369)		

Sequence	Comments	
Human fibronectin (SEQ ID NO:370)		
Human ECMproBM40 (SEQ ID NO:371)		
Human collagen (SEQ ID NO:372)		
Human alpha enolase (SEQ ID NO:373)		
Human aldolase (SEQ ID NO:374)		
Human transf growth factor BIG H3 (SEQ ID NO:375)		
Human SPARC osteonectin (SEQ ID NO:376)		
Human SLP1 leucocyte protease (SEQ ID NO:377)		
Human mitochondrial ATP synth (SEQ ID NO:378)		
Human DNA seq clone 461P17 (SEQ ID NO:379)		
Human dbpB pro Y box (SEQ ID NO:380)		
Human 40 kDa keratin (SEQ ID NO:381)		
Human arginosuccinate synth (SEQ ID NO:382)		
Human acidic ribosomal phosphoprotein (SEQ ID NO:383)		
Human colon carcinoma laminin binding pro (SEQ ID NO:384)		

This screen further identified multiple forms of the clone O772P, referred to herein as 21013, 21003 and 21008. PSORT analysis indicates that 21003 (SEQ ID NO:386; translated as SEQ ID NO:389) and 21008 (SEQ ID NO:387; translated as SEQ ID NO:390) represent Type 1a transmembrane protein forms of O772P. 21013 (SEQ ID NO:385; translated as SEQ ID NO:388) appears to be a truncated form of the protein and is predicted by PSORT analysis to be a secreted protein.

Additional sequence analysis resulted in a full length clone for O8E (2627 bp, which agrees with the message size observed by Northern analysis; SEQ ID NO:391). This nucleotide sequence was obtained as follows: the original O8E sequence (OrigO8Econs) was found to overlap by 33 nucleotides with a sequence from an EST clone (IMAGE#1987589). This clone provided 1042 additional nucleotides upstream of the original O8E sequence. The link between the EST and O8E was confirmed by sequencing multiple PCR fragments generated from an ovary primary tumor library using primers to the unique EST and the O8E sequence (ESTxO8EPCR). Full length status was further indicated when anchored PCR from the ovary tumor library gave

several clones (AnchoredPCR cons) that all terminated upstream of the putative start methionine, but failed to yield any additional sequence information. Figure 16 presents a diagram that illustrates the location of each partial sequence within the full length O8E sequence.

Two protein sequences may be translated from the full length O8E. For "a" (SEQ ID NO:393) begins with a putative start methionine. A second form "b" (SEQ ID NO:392) includes 27 additional upstream residues to the 5' end of the nucleotide sequence.

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EXAMPLE 3

This example discloses the identification and characterization of antibody epitopes recognized by the O8E polyclonal anti-sera.

Rabbit anti-sera was raised against E. coli derived O8E recombinant protein and tested for antibody epitope recognition against 20 or 21 mer peptides that correspond to the O8E amino acid sequence. Peptides spanning amino acid regions 31 to 65, 76 to 110, 136 to 200 and 226 to 245 of the full length O8E protein were recognized by an acid eluted peak and/or a salt eluted peak from affinity purified anti-O8E sera. Thus, the corresponding amino acid sequences of the above peptides constitute the antibody epitopes recognized by affinity purified anti-O8E antibodies.

ELISA analysis of anti-08E rabbit sera is shown in Figure 23, and ELISA analysis of affinity purified rabbit anti-08E polyclonal antibody is shown in Figure 24.

For epitope mapping, 20 or 21 mer peptides corresponding to the O8E protein were synthesized. For antibody affinity purification, rabbit anti-O8E sera was run over an O8E-sepharose column, then antibody was eluted with a salt buffer containing 0.5 M NaCl and 20 mM PO₄, followed by an acid elution step using 0.2 M Glycine, pH 2.3. Purified antibody was neutralized by the addition of 1M Tris, pH 8 and buffer exchanged into phosphate buffered saline (PBS). For enzyme linked immunosorbant assay (ELISA) analysis, O8E peptides and O8E recombinant protein were coated onto 96 well flat bottom plates at 2 μg/ml for 2 hours at room temperature (RT). Plates were then washed 5 times with PBS + 0.1 % Tween 20 and blocked with PBS + 1 % bovine serum albumin (BSA) for 1 hour. Affinity purified anti-O8E antibody, either an acid or salt eluted fraction, was then added to the wells at 1 μg/ml

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and incubated at RT for 1 hr. Plates were again washed, followed by the addition of donkey anti-rabbit-Ig-horseradish peroxidase (HRP) antibody for 1 hour at RT. Plates were washed, then developed by the addition of the chromagenic substrate 3, 3', 5, 5'-tetramethylbenzidine (TMB) (described by Bos et al., J. of Immunoassay 2:187-204 (1981); available from Sigma (St. Louis, MO)). The reaction was incubated 15 minutes at RT and then stopped by the addition of 1 N H₂SO₄. Plates were read at an optical density of 450 (OD450) in an automated plate reader. The sequences of peptides corresponding to the OE8 antibody epitopes are disclosed herein as SEQ ID NO: 394-415. Antibody epitopes recognized by the O8E polyclonal anti-sera are disclosed herein in Figure 17.

EXAMPLE 4

This example discloses IHC analysis of O8E expression in ovarian cancer tissue samples.

For immunohistochemistry studies, paraffin-embedded formalin fixed ovarian cancer tissue was sliced into 8 micron sections. Steam heat induced epitope retrieval (SHIER) in 0.1 M sodium citrate buffer (pH 6.0) was used for optimal staining conditions. Sections were incubated with 10% serum/PBS for 5 minutes. Primary antibody (anti-O8E rabbit affinity purified polyclonal antibody) was added to each section for 25 min followed by a 25 min incubation with an anti-rabbit biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 min incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase system was used along with DAB chromogen to visualize antigen expression. Slides were counterstained with hematoxylin. One (papillary serous carcinoma) of six ovarian cancer tissue sections displayed O8E immunoreactivity. Upon optimization of the staining conditions, 4/5 ovarian cancer samples stained positive using the O8E polyclonal antibody. O8E expression was localized to the plasma membrane.

Six ovarian cancer tissues were analyzed with the anti-O8E rabbit polyclonal antibody. One (papillary serous carcinoma) of six ovarian cancer tissue samples stained positive for O8E expression. O8E expression was localized to the surface membrane.

EXAMPLE 5

This example discloses O8E peptides that are predicted to bind HLA-A2 and to be immunogenic for CD8 T cell responses in humans.

Potential HLA-A2 binding peptides of O8E were predicted by using the full-length open-reading frame (ORF) from O8E and running it through "Episeek," a program used to predict MHC binding peptides. The program used is based on the algorithm published by Parker, K.C. et al., J. Immunol. 152(1):163-175 (1994) (incorporated by reference herein in its entirety). 10-mer and 9-mer peptides predicted to bind HLA-0201 are disclosed herein as SEQ ID NO: 416-435 and SEQ ID NO: 436-455, respectively.

EXAMPLE 6

This example discloses O8E cell surface expression measured by fluoresence activated cell sorting.

For FACS analysis, cells were washed with ice cold staining buffer (PBS/1% BSA/azide). Next, the cells were incubated for 30 minutes on ice with 10 micrograms/ml of affinity purified rabbit anti-B305D polyclonal antibody. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig (H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing prodium iodide, a vital stain that allows for identification of permeable cells, and analyzed by FACS. O8E surface expression was confirmed on SKBR3 breast cancer cells and HEK293 cells that stably overexpress the cDNA for O8E. Neither MB415 cells nor HEK293 cells stably transfected with a control irrelevant plasmid DNA showed surface expression of O8E (Figures 18 and 19).

25 EXAMPLE 7

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This example further evaluates the expression and surface localization of O8E.

For expression and purification of antigen used for immunization, O8E expressed in an E. coli recombinant expression system was grown overnight in LB Broth with the appropriate antibiotics at 37°C in a shaking incubator. The next morning,

10 ml of the overnight culture was added to 500 ml of 2x YT plus appropriate antibiotics in a 2L-baffled Erlenmeyer flask. When the Optical Density (at 560 nanometers) of the culture reached 0.4-0.6 the cells were induced with IPTG (1 mM). 4 hours after induction with IPTG the cells were harvested by centrifugation. The cells were then washed with phosphate buffered saline and centrifuged again. The supernatant was discarded and the cells were either frozen for future use or immediately processed. Twenty milliliters of lysis buffer was added to the cell pellets and vortexed. To break open the E. coli cells, this mixture was then run through the French Press at a pressure of 16,000 psi. The cells were then centrifuged again and the supernatant and pellet were checked by SDS-PAGE for the partitioning of the recombinant protein. For 10 protein that localized to the cell pellet, the pellet was resuspended in 10 mM Tris pH 8.0 , 1% CHAPS and the inclusion body pellet was washed and centrifuged again. This procedure was repeated twice more. The washed inclusion body pellet was solubilized with either 8 M urea or 6 M guanidine HCl containing 10 mM Tris pH 8.0 plus 10 mM imidazole. The solubilized protein was added to 5 ml of nickel-chelate resin (Qiagen) 15 and incubated for 45 min to 1 hour at room temperature with continuous agitation. After incubation, the resin and protein mixture were poured through a disposable column and the flow through was collected. The column was then washed with 10-20 column volumes of the solubilization buffer. The antigen was then eluted from the column using 8M urea, 10 mM tris pH 8.0 and 300 mM imidazole and collected in 3 ml fractions. A SDS-PAGE gel was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin such as Hi-Prep Q (Biorad) was equilibrated with the appropriate buffer and the pooled fractions from above were loaded onto the column. Each antigen was eluted off of the column with an increasing salt gradient. Fractions were collected as the column was run and another SDS-PAGE gel was run to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10 mM Tris pH 8.0. This material was then evaluated for acceptable purity as determined by SDS-PAGE or HPLC, concentration as determined by Lowry assay or Amino Acid Analysis, identity as determined by amino terminal protein sequence, and endotoxin level as determined by the Limulus (LAL) assay. The proteins were then vialed after filtration through a 0.22 micron filter and the antigens were frozen until needed for immunization.

For generation of polyclonal anti-sera, 400 micrograms of each prostate antigen was combined with 100 micrograms of muramyldipeptide (MDP). Equal volume of Incomplete Freund's Adjuvant (IFA) was added and then mixed. Every four weeks animals were boosted with 100 micrograms of antigen mixed with an equal volume of IFA. Seven days following each boost the animal was bled. Sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

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For characterization of polyclonal antisera, 96 well plates were coated with antigen by incubating with 50 microliters (typically 1 microgram) at 4°C for 20 hrs. 250 microliters of BSA blocking buffer was added to the wells and incubated at RT for 2 hrs. Plates were washed 6 times with PBS/0.01% tween. Anti-O8E rabbit sera or affinity purified anti-O8e antibody was diluted in PBS. Fifty microliters of diluted antibody was added to each well and incubated at RT for 30 min. Plates were washed as described above before 50 microliters of goat anti-rabbit horse radish peroxidase (HRP) at a 1:10000 dilution was added and incubated at RT for 30 min. Plates were washed as described above and 100 microliters of TMB microwell Peroxidase Substrate was added to each well. Following a 15 minute incubation in the dark at room temperature the colorimetric reaction was stopped with 100 microliters of 1N H2SO4 and read immediately at 450 nm. All polyclonal antibodies showed immunoreactivity to the O8E antigen.

For recombinant expression in mammalian HEK293 cells, full length O8E cDNA was subcloned into the mammalian expression vectors pcDNA3.1+ and pCEP4 (Invitrogen) which were modified to contain His and FLAG epitope tags, respectively. These constructs were transfected into HEK293 cells (ATCC) using Fugene 6 reagent (Roche). Briefly, HEK293 cells were plated at a density of 100,000 cells/ml in DMEM (Gibco) containing 10% FBS (Hyclone) and grown overnight. The following day, 2 ul of Fugene6 was added to 100 ul of DMEM containing no FBS and incubated for 15 minutes at room temperature. The Fugene6/DMEM mixture was then added to 1ug of O8E/pCEP4 or O8E/pcDNA3.1 plasmid DNA and incubated for 15 minutes at room temperature. The Fugene/DNA mix was then added to the HEK293

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cells and incubated for 48-72 hrs at 37oC with 7% CO2. Cells were rinsed with PBS then collected and pelleted by centrifugation. For Western blot analysis, whole cell lysates were generated by incubating the cells in Triton-X100 containing lysis buffer for 30 minutes on ice. Lysates were then cleared by centrifugation at 10,000rpm for 5 minutes at 4 C. Samples were diluted with SDS-PAGE loading buffer containing beta-mercaptoethanol, then boiled for 10 minutes prior to loading the SDS-PAGE gel. Protein was transferred to nitrocellulose and probed using anti-O8E rabbit polyclonal sera #2333L at a dilution of 1:750. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate.

For FACS analysis, cells were washed further with ice cold staining buffer (PBS+1%BSA+Azide). Next, the cells were incubated for 30 minutes on ice with 10ug/ml of Protein A purified anti-O8E polyclonal sera. The cells were washed 3 times with staining buffer and then incubated with a 1:100 dilution of a goat anti-rabbit Ig(H+L)-FITC reagent (Southern Biotechnology) for 30 minutes on ice. Following 3 washes, the cells were resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that allows for the identification of permeable cells, and analyzed by FACS.

From these experiments, the results of which are illustrated in Figures 20-21, O8E expression was detected on the surface of transfected HEK293 cells and SKBR3 cells by FACS analysis using rabbit anti-O8E sera. Expression was also detected in transfected HEK293 cell lysates by Western blot analysis (Figure 22).

EXAMPLE 8

GENERATION AND CHARACTERIZATION OF ANTI-O8E MABS.

Mouse monoclonal antibodies were raised against E. coli derived O8E proteins as follows. A/J mice were immunized intraperitoneally (IP) with Complete Freund's Adjuvant (CFA) containing 50 µg recombinant O8E, followed by a subsequent IP boost with Incomplete Freund's Adjuvant (IFA) containing 10µg recombinant O8E protein. Three days prior to removal of the spleens, the mice were immunized intravenously with approximately 50µg of soluble O8E recombinant protein. The spleen of a mouse with a positive titer to O8E was removed, and a single-cell suspension made and used for fusion to SP2/0 myeloma cells to generate B cell

hybridomas. The supernatants from the hybrid clones were tested by ELISA for specificity to recombinant O8E, and epitope mapped using peptides that spanned the entire O8E sequence. The mAbs were also tested by flow cytometry for their ability to detect O8E on the surface of cells stably transfected with O8E and on the surface of a breast tumor cell line.

For ELISA analysis, 96 well plates were coated with either recombinant O8E protein or overlapping 20-mer peptides spanning the entire O8E molecule at a concentration of either 1-2µg/ml or 10µg/ml, respectively. After coating, the plates were washed 5 times with washing buffer (PBS + 0.1% Tween-20) and blocked with PBS containing 0.5% BSA, 0.4% Tween-20. Hybrid supernatants or purified mAbs were then added and the plates incubated for 60 minutes at room temperature. The plates were washed 5 times with washing buffer and the secondary antibody, donkey-anti mouse Ig linked to horseradish peroxidase (HRP)(Jackson ImmunoResearch), was added for 60 minutes. The plates were again washed 5 times in washing buffer, followed by the addition of the peroxidase substrate. Of the hybridoma clones generated, 15 secreted mAbs that recognized the entire O8E protein. Epitope mapping revealed that of these 15 clones, 14 secreted mAbs that recognized the O8E amino acid residues 61-80 and one clone secreted a mAb that recognized amino acid residues 151-170.

For flow cytometric analysis, HEK293 cells which had been stably transfected with O8E and SKBR3 cells which express O8E mRNA, were harvested and washed in flow staining buffer (PBS+1%BSA+Azide). The cells were incubated with the supernatant from the mAb hybrids for 30 minutes on ice followed by 3 washes with staining buffer. The cells were incubated with goat-anti mouse Ig-FITC for 30 minutes on ice, followed by three washes with staining buffer before being resuspended in wash buffer containing propidium iodide. Flow cytometric analysis revealed that 15/15 mAbs were able to detect O8E protein expressed on the surface of O8E-transfected HEK293 cells. 6/6 mAbs tested on SKBR3 cells were able to recognize surface expressed O8E.

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EXAMPLE 9

EXTENDED DNA AND PROTEIN SEQUENCE ANALYSIS OF SEQUENCE O772P

A full-length sequence encompassing clones 3f, 6b, 8e, and 12 was obtained by screening an ovarian tumor (SCID-derived) cDNA library described in 5 detail in Example 2. This 2996 base pair sequence, designated O772P, is presented in SEQ ID NO: 311, and the encoded 914 amino acid protein sequence is shown in SEQ ID NO: 312. The DNA sequence O772P was searched against public databases including Genbank and showed a significant hit to Genbank Accession number AK024365 (SEQ ID NO: 457). This Genbank sequence was found to be 3557 base pairs in length and encodes a protein 1156 amino acids in length (SEQ ID NO: 459). A truncated version of this sequence, residues 25-3471, in which residue 25 corresponds to the first ATG initiation codon in the Genbank sequence, (SEQ ID NO: 456), encodes a protein that is 1148 amino acids in length (SEQ ID NO: 458). The published DNA sequence (SEQ ID NO: 457) differs from O772P in that it has a 5 base pair insertion corresponding to bases 958-962 of SEQ ID NO: 457. This insertion results in a frame 15 shift such that SEQ ID NO: 457 encodes an additional N-terminal protein sequence relative to O772P (SEQ ID NO: 312). In addition, O772P encodes a unique N-terminal portion contained in residues 1-79 (SEQ ID NO: 460). The N-terminal portion of SEQ ID NO: 456, residues 1-313, also contains unique sequence and is listed as SEQ ID NO: 20 461.

EXAMPLE 10

THE GENERATION OF POLYCLONAL ANTIBODIES FOR IMMUNOHISTOCHEMISTRY AND FLOW CYTOMETRIC ANALYSIS OF THE CELL ASSOCIATED EXPRESSION PATTERN OF MOLECULE O772P

The O772P molecule was identified in Examples 2 and 9 of this To evaluate the subcellular localization and specificity of antigen application. expression in various tissues, polyclonal antibodies were generated against O772P. To produce these antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312) were expressed in an E. coli recombinant expression system and grown overnight at 37°C in LB Broth. The following day, 10ml of the overnight culture was added to 500ml of 2xYT containing the appropriate antibiotics. When the optical density of the cultures (560 nanometers) reached 0.4-0.6 the cells were induced with IPTG. Following induction, the cells were harvested, washed, lysed and run through a French Press at a pressure of 16000 psi. The cells were then centrifuged and the pellet checked by SDS-PAGE for the partitioning of the recombinant protein. For proteins that localize to the cell pellet, the pellet was resuspended in 10mM Tris, pH 8.0, 1% CHAPS and the inclusion body pellet washed and centrifuged. The washed inclusion body was solubilized with either 8M urea or 6M guanidine HCL containing 10mM Tris, pH 8.0, plus 10mM imidazole. The solubilized protein was then added to 5ml of nickel-chelate resin (Qiagen) and incubated for 45 minutes at room temperature.

Following the incubation, the resin and protein mixture was poured through a column and the flow through collected. The column was washed with 10-20 column volumes of buffer and the antigen eluted using 8M urea, 10mM Tris, pH 8.0, and 300 mM imidazole and collected in 3ml fractions. SDS-PAGE was run to determine which fractions to pool for further purification. As a final purification step, a strong anion exchange resin was equilibrated with the appropriate buffer and the pooled fractions were loaded onto the column. Each antigen was eluted from the column with an increasing salt gradient. Fractions were collected and analyzed by a SDS-PAGE to determine which fractions from the column to pool. The pooled fractions were dialyzed against 10mM Tris, pH 8.0, and the resulting protein was submitted for quality control for final release. The release criteria were: (a) purity as determined by SDS-PAGE or HPLC, (b) concentration as determined by Lowry assay or Amino Acid Analysis, (c) identity as determined by amino terminal protein, and (d) endotoxin levels as determined by the Limulus (LAL) assay. The proteins were then filtered through a 0.22µM filter and frozen until needed for immunizations.

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To generate polyclonal antisera, 400µg of O772P-1 or O772P-2 was combined with 100µg of muramyldipeptide (MDP). The rabbits were immunized every 4 weeks with 100µg of antigen mixed with an equal volume of Incomplete Freund's Adjuvant (IFA). Seven days following each boost, the animals were bled and sera was generated by incubating the blood at 4°C for 12-24 hours followed by centrifugation.

To characterize the antisera, 96 well plates were coated with antigen followed by blocking with BSA. Rabbit sera was diluted in PBS and added to each well. The plates were then washed, and goat anti-rabbit horseradish peroxidase (HRP). The plates were again washed and TMB microwell Peroxidase Substrate was added. Following this incubation, the colormetric reaction was stopped and the plates read immediately at 450nm. All polyclonal antibodies showed immunoreactivity to the appropriate antigen.

Immunohistochemistry analysis of O772P expression was performed on paraffin-embedded formalin fixed tissue. O772P was found to be expressed in normal ovary and ovarian tumor, but not in normal heart, kidney, colon, lung or liver. Additionally, immunohistochemistry and flow cytometric analysis indicates that O772P is a plasma membrane-associated molecule. O772P contains 1 plasma transmembrane domain predicted to be encoded by amino acids 859-880. The N-terminus of O772P is extracellular and is encoded by amino acids 1-859, while the C-terminus is intracellular. Sequence analysis shows that there are 17 potential N-linked glycosylation sites.

EXAMPLE 11

O772P IS EXPRESSED ON THE SURFACE OF PRIMARY OVARIAN TUMOR CELLS

For recombinant expression in mammalian cells, the O772P-21008 (SEQ ID NO:387) and O772P full length cDNA (SEQ ID NO:311 encoding the protein of SEQ ID NO:312) were subcloned into mammalian expression vectors pBIB or pCEP4 respectively. These constructs were transfected into HEK293 cells using Fugene 6 (Roche). The HEK cells were then plated at a density of 100,000 cells/ml in DMEM containing fetal bovine serum (FBS) and grown overnight. The following day, 2μl of Fugene 6 was added to 100μl of DMEM, which contained no FBS, and incubated for 15 minutes at room temperature. The Fugene 6/DMEM mixture was then added to 1μg of O772P/pBIB or O772P/pCEP4 plasmid DNA and incubated for an additional 15 minutes at room temperature. The Fugene 6/DNA mix was then added to the HEK293 cells and incubated for 48-72 hours at 37°C with 7% CO₂. The cells were rinsed and pelleted by centrifugation.

For Western Blot analysis, whole cell lysates were generated by incubating the cells in lysis buffer followed by clarification by centrifugation. The samples were diluted and run on SDS-PAGE. The gel was then transferred to nitrocellulose and probed using purified anti-O772P-2 rabbit polyclonal antibody. The blot was revealed with a goat anti-rabbit Ig coupled to HRP followed by incubation in ECL substrate. Western Blot analysis revealed that O772P-21008 could be detected in HEK293 cells that had been transfected with O772P.

To determine the cell expression profile of O772P in cells, primary ovarian tumor cells were grown in SCID mice. The cells were retrieved from the mice and analyzed by flow cytometry. Briefly, cells washed in cold staining buffer containing PBS, 1% BSA, and Na Azide. The cells were incubated for 30 minutes with 10μg/ml of purified anti-O772P-1 and O772P-2 polyclonal sera. Following this incubation, the cells were washed three times in staining buffer and incubated with goat anti-rabbit Ig (H+L) conjugated to FITC (Southern Biotechnology). The cells were washed and resuspended in staining buffer containing Propidium Iodide (PI), a vital stain that identifies non-viable cells. The cells were then analyzed using Fluorescence Activated Cell Sorting (FACS). FACS analysis revealed that O772P was present on the cells surface. Surface expression of O772P on tumor cells allows for immune targeting by therapeutic antibodies.

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EXAMPLE 12

FUNCTIONAL CHARACTERIZATION OF ANTI-O8E MONOCLONAL ANTIBODIES

Mouse monoclonal antibodies (mAb) raised against E. coli derived O8E, as described in Example 8, were tested for their ability to promote O8E antigen internalization. Internalization of the antibody was determined using an in vitro cytotoxicity assay. Briefly, HEK293 and O8E/HEK transfected cells were plated into 96 well plates containing DME plus 10% heat-inactivated FBS in the presence of 50ng/well of purified anti-O8E or control antibodies. The isotype of the anti-O8E mAbs are as follows: 11A6-IgG1/kappa, 15C6-IgG2b/kappa, 18A8-IgG2b/kappa, and 14F1-IgG2a/kappa. W6/32 is a pan anti-human MHC class I mouse monoclonal antibody that serves as a positive control, and two irrelevant mAbs, Ir-Pharm and Ir-

Crxa were included as negative controls. Following incubation with the O8E specific antibodies or the relevant controls antibodies, the mAb-zap, a goat anti-mouse Igsaporin conjugated secondary antibody (Advanced Targeting Systems) was added at a concentration of 100ng/ml to half of the wells, and the plates were incubated for 48 to 72 hours at 37°C in a 7% CO₂ incubator. This assay takes advantage of the toxic nature of saporin, a ribozyme inactivating protein, which when internalized has a cytotoxic effect. Following incubation with the mAb-zap, internalization was quantitated by the addition of MTS reagent, followed by reading the OD490 of the plate on a microplate ELISA reader. Figure 25 depicts the results from these assays. The top panel represents HEK cells that have not been transfected with O8E and therefore O8E antibody should not bind and be internalized. Levels of proliferation were the same in all samples whether they were incubated with or without the mAb-zap, with the exception of the positive control Ab, W6/32. The lower panel represents cells that have been transfected with O8E and therefore should bind O8E specific antibodies. Antibodies from the hybridomas 11H6, 14F1, and 15C6, which recognize the amino acids 61-80 of O8E 15 were able to promote internalization of the O8E surface protein as measured by decreased levels of proliferation due to the toxic nature of the mAb-zap (See Figure 25). The antibody generated by the hybridoma 18A8, which recognizes amino acids 151-170 of O8E, was unable to promote internalization as determined by normal levels of proliferation either in the absence or presence of the mAb-zap.

EXAMPLE 13

CHARACTERIZATION OF THE OVARIAN TUMOR ANTIGEN, O772P

The cDNA and protein sequences for multiple forms of the ovarian tumor antigen O772P have been described in the above (e.g., Examples 2 and 9). A Genbank search indicated that O772P has a high degree of similarity with FLJ14303 (Accession # AK024365; SEQ ID NO:457 and 463). Protein sequences corresponding to O772P and FLJ14303 are disclosed in SEQ ID NO:478 and 479, respectively. FLJ14303 was identical to the majority of O772P, with much of the 3'-end showing 100% homology. However, the 5'-end of FLJ14303 was found to extend further 5' than O772P. In addition, FLJ14303 contained a 5 bp insert (SEQ ID NO:457) resulting in a

frame shift of the amino-terminus protein sequence such that FLJ14303 utilizes a different starting methionine than O772P and therefore encodes a different protein. This insertion was present in the genomic sequence and seen in all EST clones that showed identity to this region, suggesting that FLJ14303 (SEQ ID NO:457) represents a splice variant of O772P, with an ORF that contains an extended and different amino-terminus. The additional 5'-nucleotide sequence included repeat sequences that were identified during the genomic mapping of O772P. The 5'-end of O772P and the corresponding region of FLJ14303 showed between 90-100% homology. Taken together, this suggests that O772P and FLJ14303 are different splice variants of the same gene, with different unique repeat sequences being spliced into the 5'-end of the gene.

The identification of an additional ten or more repeat sequences within the same region of chromosome 19, indicates that there may be many forms of O772P, each with a different 5'-end, due to differential splicing of different repeat sequences. Northern blot analysis of O772P demonstrated multiple O772P-hybridizing transcripts of different sizes, some in excess 10kb.

Upon further analysis, 13 additional O772P-related sequences were identified, the cDNA and amino acid sequences of which are described in Table 2.

Table 2

SEQ ID NO:	Description	Transmembrane Domains
464	LS #1043400.1 (cDNA)	nd
465 LS #1043400.10 (cDNA) 0		0
466	LS #1043400.11 (cDNA)	2
467	LS #1043400.12 (cDNA)	2
468	LS #1043400.2 (cDNA)	nd
469	LS #1043400.3 (cDNA)	
470	LS #1043400.5 (cDNA)	nd
471	LS #1043400.8 (cDNA)	1
472	LS #1043400.9 (cDNA)	0 .

473	LS #1043400.6 (cDNA)	nd
474	LS #1043400.7 (cDNA)	nd
475	LS #1043400.4 (cDNA)	nd
476	LS #1397610.1 (cDNA)	0
477	1043400.10 Novel 5' (cDNA)	-
480	LS #1043400.9 (amino acid)	-
481	LS #1043400.8B (amino acid)	-
]	Contains a transmembrane	
	domain	
482	LS #1043400.8A (amino acid)	•
483	LS #1043400.12 (amino acid)	-
	Contains a transmembrane	
	domain	
484	LS #1043400.11B (amino acid)	-
r	Contains a transmembrane	
	domain	
485	LS #1043400.11A (amino acid)	-
486	LS #1043400.10 (amino acid)	-
487	LS #1043400.1 (amino acid)	

nd=not determined

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Initially it appeared that these sequences represented overlapping and/or discrete sequences of O772P splice forms that were capable of encoding polypeptides unique to the specific splice forms of O772P. However, nucleotide alignment of these sequences failed to identify any identical regions within the repeat elements. This indicates that the sequences may represent different specific regions of a single O772P gene, one that contains 16 or more repeat domains, all of which form a single linear transcript. The 5'-end of sequence LS #1043400.10 (Table 2; SEQ ID NO:465) is unique to both O772P and FLJ14303 and contains no repeat elements, indicating that this sequence may represent the 5'-end of O772P.

Previously, transmembrane prediction analysis had indicated that O772P contained between 1 and 3 transmembrane spanning domains. This was verified by the

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use of immunohistochemistry and flow cytometry, which demonstrated the existence of a plasma membrane-associated molecule representing O772P. However, immunohistochemistry also indicated the presence of secreted form(s) of O772P, possibly resulting from an alternative splice form of O772P or from a post-translational cleavage event. Analysis of several of the sequences presented in Table 2 showed that sequences 1043400B.12, 1043400.8B, and 1043400.11B all contained transmembrane regions, while 1043400.8A, 1043400.10, 1043400.1, 1043400.11A, and 1043400.9 were all lacking transmembrane sequences, suggesting that these proteins may be secreted.

Analysis indicates a part of O772P is expressed and/or retained on the plasma membrane, making O772P an attractive target for directing specific immunotherapies, e.g., therapeutic antibodies, against this protein. The predicted extracellular domain of O772P is disclosed in SEQ ID NO:489 and secretion of O772P is likely to occur as a result of a cleavage event within the sequence:

 ${\tt SLVEQVFLD}\underline{\textit{K}}{\tt TLNASFHWLGSTYQLVDIHVTEMESSVYQP}.$

Proteolytic cleavage is most likely to occur at the Lysine (K) at position 10 of SEQ ID NO:489. The extracellular, transmembrane, and cytoplasmic regions of O772P are all disclosed in SEQ ID NO:488:

Extracellular:

20 SLVEQVFLDKTLNASFHWLGSTYQLVDIHVTEMESSVYQPTSSSS
TQHFYLNFTITNLPYSQDKAQPGTTNYQRNKRNIEDALNQLFRNSSIKSYFSDCQ
VSTFRSVPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDR
SSVLVDGYFPNRNEPLTGNSDLPF

Transmembrane:

25 WAVILIGLAGLIGLITCLICGVLVTT

Cytoplasmic:

RRRKKEGEYNVQQQCPGYYQSHLDLEDLQ

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EXAMPLE 14

IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS OF O8E EXPRESSION IN OVARIAN CANCER AND NORMAL TISSUES

In order to determine which tissues express the ovarian cancer antigen 5 O8E, IHC analysis was performed on a diverse range of tissue sections using both polyclonal and monoclonal antibodies specific for O8E. The generation of O8E specific polyclonal antibodies is described in detail in Example 8. The monoclonal antibodies used for staining were 11A6 and 14F1, both of which are specific for amino acids 61-80 of O8E and 18A8, which recognizes amino acids 151-170 of O8E (see Example 12 for details on generation).

To perform staining, tissue samples were fixed in formalin solution for 12-24 hours and embedded in paraffin before being sliced into 8 micron sections. Steam heat induced epitope retrieval (SHEIR) in 0.1M sodium citrate buffer (pH 6.0) Sections were incubated with 10% was used for optimal staining conditions. serum/PBS for 5 minutes. Primary antibody was then added to each section for 25 minutes followed by 25 minutes of incubation with either anti-rabbit or anti-mouse biotinylated antibody. Endogenous peroxidase activity was blocked by three 1.5 minute incubations with hydrogen peroxidase. The avidin biotin complex/horse radish peroxidase (ABC/HRP) system was used along with DAB chromogen to visualize the 20 antigen expression. Slides were counterstained with hematoxylin to visualize the cell nuclei.

Results using rabbit affinity purified polyclonal antibody to O8E (a.a. 29-283; for details on the generation of this Ab, see Example 3) are presented in Table 3. Results using the three monoclonal antibodies are presented in Table 4.

Table 3 Immunohistochemistry analysis of O8E using polyclonal antibodies

Tissue	O8E Expression
Ovarian Cancer	Positive
Breast Cancer	Positive

Normal Ovary	Positive
Normal Breast	Positive
Blood Vessel	Positive
Kidney	Negative
Lung	Negative
Colon	Negative
Liver	Negative
Heart	Negative

<u>Table 4</u>
<u>Immunohistochemistry analysis of O8E using monoclonal antibodies</u>

Normal	11/	A 6	18.4	78	14I	71
Tissue	Endothelia	Epithelial	Endothelial	Epithelial	Endothelial	Epithelial
	1				•	
Skin	2	2	0	0	1	1
Skin	1	1	0	0	1	1
Breast	0	1	n/a	n/a	1	1
Colon	0	0	0	0	0	0
Jejunum	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Colon	0	0	0	0	0	0
Ovary	0	0	0	0	1	0 .
Colon	0	0	0	0	0	1
Liver	0	0	0	0	1	2
Skin	0	0	0	0	1	0
Duodenum	0	0	0	o	0	0
and Pancreas						
Appendix	0	0	0	0	0	0
Ileum	0	0	0	0	0	0

0=no staining, 1=light staining, 2=moderate staining, n/a=not available

20

80

EXAMPLE 15

EPITOPE MAPPING OF O772P POLYCLONAL ANTIBODIES

To perform epitope mapping of O772P, peptides were generated, the sequences of which were derived from the sequence of O772P. These peptides were 15 mers that overlapped by 5 amino acids and were generated via chemical synthesis on membrane supports. The peptides were covalently bound to Whatman 50 cellulose support by their C-terminus with the N-terminus unbound. In order to determine epitope specificity, the membranes were wet with 100% ethanol for 1 minute, and then blocked for 16 hours in TBS/Tween/Triton buffer (50mM Tris, 137 mM NaCl, 2.7 mM KCl, 0.5% BSA, 0.05% Tween 20, 0.05% Triton X-100, pH 7.5). The peptides were then probed with 2 O772P specific antibodies, O772P-1 (amino acids 44-772 of SEQ ID NO:312) and O772P-2 (477-914 of SEQ ID NO:312; see Example 10 for details of antibody generation), as well as irrelevant rabbit antibodies for controls. The antibodies were diluted to 1µg/ml and incubated with the membranes for 2 hours at room temperature. The membranes were then washed for 30 minutes in TBS/Tween/Triton buffer, prior to being incubated with a 1:10,000 dilution of HRP-conjugated anti-rabbit secondary antibody for 2 hours. The membranes were again washed for 30 minutes in TBS/Tween/Triton and anti-peptide reactivity was visualized using ECL. Specific epitope binding specificity for each of the O772P-polyclonal antibodies is described in Table 5.

Table 5

SEQ ID NO:	Peptide #	Anti-O772P1	Anti-O772P2	Peptide Sequence
490	2	***	-	TCGMRRTCSTLAPGS
491	6	*	*/-	CRLTLLRPEKDGTAT
492	7	*	-	DGTATGVDAICTHHP
493	8	-	-	CTHHPDPKSPRLDRE
494	9	***	***	RLDREQLYWELSQLT
495	11	*/-	-	LGPYALDNDSLFVNG
496	13	****	-	SVSTTSTPGTPTYVL
497	22	 	-	LRPEKDGEATGVDAI
498	24	**	*/-	DPTGPGLDREQLYLE
499	27	*/-	 	LDRDSLYVNGFTHRS
500	40	*/-	-	GPYSLDKDSLYLNGY
501	41	 	 	YLNGYNEPGPDEPPT
502	47	***	***	ATFNSTEGVLQHLLR

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503	50	-	***	QLISLRPEKDGAATG
504	51	-	**	GAATGVDTTCTYHPD
505	52	_	*/-	TYHPDPVGPGLDIQQ
506	53	-	*	LDIQQLYWELSQLTH
507	58	-	*	HIVNWNLSNPDPTSS
508	59	-	*	DPTSSEYITLLRDIQ
509	60	_	*	LRDIQDKVTTLYKGS
510	61	-	***	LYKGSQLHDTFRFCL
511	71	-	**	DKAQPGTTNYQRNKR

^{*=} relative reactive level, -; no binding, ****; maximal binding

5

10

20

25

EXAMPLE 16 IDENTIFICATION OF A NOVEL N-TERMINAL REPEAT STRUCTURE ASSOCIATED WITH 0772P

Various O772P cDNA and protein forms have been identified and characterized as detailed above (e.g., Examples 1, 2, 9, and 14). Importantly, O772P RNA and protein have been demonstrated to be over-expressed in ovarian cancer tissue relative to normal tissues and thus represents an attractive target for ovarian cancer diagnostic and therapeutic applications.

Using bioinformatic analysis of open reading frames (ORFs) from genomic nucleotide sequence identified previously as having homology with O772P, multiple nucleotide repeat sequences were identified in the 5' region of the gene encoding the O772P protein. A number of these repeat sequences were confirmed by RT-PCR using primers specific for the individual repeats. Fragments which contained multiple repeats were amplified from cDNA, thus confirming the presence of specific repeats and allowing an order of these repeats to be established.

Unexpectedly, when various sets of O772P sequences derived from different database and laboratory sources were analyzed, at least 20 different repeat structures, each having substantial levels of identity with each other (see Table 6), were identified in the 5' region of the O772P gene and the corresponding N-terminal region of the O772P protein. Each repeat comprises a contiguous open reading frame encoding a polypeptide unit that is capable of being spliced to one or more other repeats such that concatomers of the repeats are formed in differing numbers and orders. Interestingly, other molecules have been described in the scientific literature that have repeating structural domains analogous to those described herein for O772P. For example, the

mucin family of proteins, which are the major glycoprotein component of the mucous which coats the surfaces of cells lining the respiratory, digestive and urogenital tracts, have been shown to be composed of tandemly repeated sequences that vary in number, length and amino acid sequence from one mucin to another (Perez-Vilar and Hill, J. Biol. Chem. 274(45):31751-31754, 1999).

The various identified repeat structures set forth herein are expected to give rise to multiple forms of O772P, most likely by alternative splicing. The cDNA sequences of the identified repeats are set forth in SEQ ID NOs:513-540, 542-546, and 548-567. The encoded amino acid sequences of the repeats are set forth in SEQ ID NOs:574-593. In many instances these amino acid sequences represent consensus sequences that were derived from the alignment of more than one experimentally derived sequence.

Each of these splice forms is capable of encoding a unique O772P protein with multiple repeat domains attached to a constant carboxy terminal protein portion of O772P that contains a trans membrane region. The cDNA sequence of the O772P constant region is set forth in SEQ ID NO:568 and the encoded amino acid sequence is set forth in SEQ ID NO:594.

All of the available O772P sequences that were obtained were broken down into their identifiable repeats and these sequences were compared using the Clustal method with weighted residue weight table (MegAlign software within DNASTAR sequence analysis package) to identify the relationship between the repeat sequences. Using this information, the ordering data provided by the RT-PCR, and sequence alignments (automatic and manual) using SeqMan (DNASTAR), one illustrative consensus full length O772P contig was identified comprising 20 distinct repeat units. The cDNA for this O772P cDNA contig is set forth in SEQ ID NO:569 and the encoded amino acid sequence is set forth in SEQ ID NO:595. This form of the O772P protein includes the following consensus repeat structures in the following order:

SEQ ID NO:572- SEQ ID NO:574- SEQ ID NO:575-SEQ ID NO:57630 SEQ ID NO:577- SEQ ID NO:578- SEQ ID NO:579- SEQ ID NO:580- SEQ ID NO:581- SEQ ID NO:582- SEQ ID NO:583- SEQ ID NO:584- SEQ ID NO:585- SEQ

ID NO:586- SEQ ID NO:587- SEQ ID NO:588- SEQ ID NO:589- SEQ ID NO:590- SEQ ID NO:591- SEQ ID NO:592- SEQ ID NO:593.

SEQ ID NO:595, therefore, represents one illustrative full-length consensus sequence for the O772P protein. As discussed above, however, based on current knowledge of this protein and based upon scientific literature describing proteins containing analogous repeating structures, many other forms of O772P are expected to exist with either more or less repeats. In addition, many forms of O772P are expected to have differing arrangements, e.g., different orders, of these N-terminal repeat structures. The existence of multiple forms of O772P having differing numbers of repeats is supported by Northern analysis of O772P. In this study, Northern hybridization of a O772P-specific probe resulted in a smear of multiple O772P-hybridizing transcripts, some in excess 10kb.

Thus, the variable repeat region of the O772 protein can be illustratively represented by the structure Xn - Y, wherein X comprises a repeat structure having at least 50% identity with the consensus repeat sequence set forth in SEQ ID NO:596; n is the number of repeats present in the protein and is expected to typically be a integer from 1 to about 35; Y comprise the O772P constant region sequence set forth in SEQ ID NO:594 or sequences having at least 80% identity with SEQ ID NO:594. Each X present in the Xn repeat region of the O772 molecule is different.

To determine the consensus sequences of each of the 20 repeat regions, sequences that were experimentally determined for a discrete repeat region were aligned and a consensus sequence determined. In addition to determining the consensus sequences for individual repeat regions, a consensus repeat sequence was also determined. This sequence was obtained by aligning the 20 individual consensus sequences. Variability of the repeats was determined by aligning the consensus amino acid sequences from each of the individual repeat regions with the over all repeat consensus sequence. Identity data is presented in Table 6.

<u>Table 6</u>

<u>Percent identities of Repeat Sequences with Reference to the Consensus Repeat Sequence</u>

Repeat Number	SEQ ID NO:	Percent Identity to
(amino acid)	•	Consensus Repeat
		Sequence
2	574	88
3	575	84
4	576	88
5	577	89
6	578	93
7	579	90
8	580	91
9	581	88
10	582	85
11	583	86
12	. 584	87
13	585	87
14	586	89
15	587	89
16	588	89
17	589	83
18	590	84
19	591	83
20	592	57
21	593	68

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration,

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various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is Claimed:

1. An O772P polypeptide having the structure:

 X_n-Y

wherein X comprises a sequence having at least 50% identity with the consensus O772P repeat sequence set forth in SEQ ID NO: 596;

Y comprises a sequence having at least 80% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 2. The polypeptide of claim 1, wherein X comprises a sequence selected from the group consisting of any one of SEQ ID NOs: 574-593.
- 3. The polypeptide of claim 1, wherein Y comprises the sequence set forth in SEQ ID NO: 594.
 - 4. The polypeptide of claim 1, wherein n is an integer from 15 to 25.
 - 5. The polypeptide of claim 1, wherein n is 20.
- 6. The polypeptide of claim 1, wherein said polypeptide comprises SEQ ID NO: 595.
- 7. The polypeptide of claim 1, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
 - 8. An O772P polypeptide having the structure:

 X_n-Y

wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 574-593;

Y comprises a sequence having at least 90% identity with the O772P constant region sequence set forth in SEQ ID NO: 594;

n is an integer from 15 to 25; wherein each X present in said polypeptide is different.

- 9. The polypeptide of claim 8, wherein n is 20.
- 10. The polypeptide of claim 8, wherein said polypeptide comprises SEQ ID NO: 595.
- 11. The polypeptide of claim 8, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.
 - 12. An O772P polypeptide having the structure:

 $X_{n}-Y$

wherein n is 20 and X comprises the following O772P repeat sequences:

SEQ ID NO: 574 - SEQ ID NO: 575 - SEQ ID NO: 576 - SEQ ID NO:

577 - SEQ ID NO: 578 - SEQ ID NO: 579 - SEQ ID NO: 580 - SEQ ID NO: 581 - SEQ

ID NO: 582 - SEQ ID NO: 583 - SEQ ID NO: 584 - SEQ ID NO: 585 - SEQ ID NO:

586 - SEQ ID NO: 587 - SEQ ID NO: 588 - SEQ ID NO: 589 - SEQ ID NO: 590 - SEQ

ID NO: 591 - SEQ ID NO: 592 - SEQ ID NO: 593; and

Y comprises the sequence set forth in SEO ID NO: 594.

- 13. The polypeptide of claim 12, wherein said polypeptide comprises SEQ ID NO: 595.
- 14. The polypeptide of claim 12, wherein said polypeptide is overexpressed in ovarian cancer cells compared with normal tissues.

15. An O772P polynucleotide having the structure:

 X_n-Y

wherein X comprises an O772P repeat sequence selected from the group consisting of any one of SEQ ID NOs: 512-540, 542-546 and 548-567;

Y comprises a sequence having at least 95% identity with the O772P constant region sequence set forth in SEQ ID NO: 568;

n is an integer from 1 to 35;

wherein each X present in said polypeptide is different.

- 16. The polynucleotide of claim 15, wherein said polynucleotide comprises SEQ ID NO: 569.
 - 17. The polynucleotide of claim 15, wherein n is from 15 to 25.
 - 18. The polynucleotide of claim 15, wherein n is 20.
- 19. The polynucleotide of claim 15, wherein said polynucleotide is overexpressed in ovarian cancer cells compared with normal tissues.
- 20. An isolated polynucleotide comprising a sequence selected from the group consisting of:
 - (a) sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (b) complements of the sequences provided in SEQ ID NOs: 464-477 and 512-569;
- (c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NOs: 464-477 and 512-569;
- (d) sequences that hybridize to a sequence provided in SEQ ID NOs: 464-477 and 512-569, under highly stringent conditions;
- (e) sequences having at least 75% identity to a sequence of SEQ ID NOs: 464-477 and 512-569;

- (f) sequences having at least 90% identity to a sequence of SEQ ID NOs: 464-477 and 512-569; and
- (g) degenerate variants of a sequence provided in SEQ ID NOs: 464-477 and 512-569.
- 21. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of: '
 - (a) sequences encoded by a polynucleotide of claim 20; and
- (b) sequences having at least 80% identity to a sequence encoded by a polynucleotide of claim 20; and
- (c) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 20.
- 22. An expression vector comprising a polynucleotide of claim 20 operably linked to an expression control sequence.
- 23. A host cell transformed or transfected with an expression vector according to claim 22.
- 24. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 21.
- 25. A method for detecting the presence of a cancer in a patient, comprising the steps of:
 - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 21;
- (c) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

- 26. A fusion protein comprising at least one polypeptide according to claim 21.
- 27. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:
 - (a) polypeptides according to claim 21;
 - (b) polynucleotides according to claim 20; and
- (c) antigen-presenting cells that express a polynucleotide according to claim 20,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 28. An isolated T cell population, comprising T cells prepared according to the method of claim 27.
- 29. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:
 - (a) polypeptides according to claim 21;
 - (b) polynucleotides according to claim 20;
 - (c) antibodies according to claim 24;
 - (d) fusion proteins according to claim 26;
 - (e) T cell populations according to claim 28; and
- (f) antigen presenting cells that express a polypeptide according to claim 21.
- 30. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 29.

- 31. A method for the treatment of a ovarian cancer in a patient, comprising administering to the patient a composition of claim 29.
- 32. A method for determining the presence of a cancer in a patient, comprising the steps of:
 - (a) obtaining a biological sample from the patient;
- (b) contacting the biological sample with an oligonucleotide that hybridizes to a polynucelotide sequence according to claim 21 under moderately stringent conditions;
- (c) detecting in the sample an amount of said polynucleotide that hybridizes to the oligonucleotide; and
- (d) comparing the amount of said polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.
- 33. An O772 polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 490-511.
- 34. An O8E polypeptide comprising at least an antibody epitope sequence set forth in any one of SEQ ID NOs: 394-415.
- 35. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 1.

1/101 11729.1 contg

11729-45.21.21.cons1

11729-45.21.21.cons2

11731.1contig

TCTTTTCTTTCGATTTCCTTCAATTTGTCACGTTTGATTTTATGAAGTTGTTCAAGGGCTAACTGCTGTGTAT
TATAGCTTTCTCTGAGGTTCCTTCAGCTGATTGTTAAATGAATCCATTTCTGAGAGCTTAGATGCAGTTTCTTTT
TCAAGAGCATCTAATTGTTCTTTAAGTCTTTGGCATAATTCTTCCTTTTCTGATGACTTTTTATGAAGTAAACT
GATCCCTGAATCAGGTGTTACTGAGCTGCATGTTTTTAATTCTTTCGTTTAATAGCTGCTTCTCAGGGACCA
GATAGATAAGCTTATTTTGATATTCCTTAAGCTCTTTGTTGAAGTTGTTTGATTTCCATAATTTCCAGGTCACAC
TGTTTATCCAAAACTTCTAGCTCAGTCTTTTTGTGTTTGCTTTCTGATTTTGGACATCTTGTAGTCTGCCTGAGAT
CTGCTGATGXTTTCCATTCACTGCTTCCAGTTCCAGGTGGAGACTTTXCTTTCTGGAGCTCAGCCTGACAATGC
CTTCTTGXTCCCT

2/101

11731.2contig

11734.1contig

AATAGATTTAATGCAGAGTGTCAACTTCAATTGATTGATAGTGGCTGCCTAGAGTGCTGTGTTGAGTAGGTTTC
TGAGGATGCACCCTGGCTTGAAGAGAAAGACTGGCAGGATTAACAATATCTAAAATCTCACTTGTAGGAGAAAC
CACAGGCACCAGAGCTGCCACTGGTGCTGGCACCAGCTCCACCAAGGCCAGCGAAGAGCCCAAATGTGAGAGTG
GCGGTCAGGCTGGCACCAGCACTGAAGCCACCACTGGTGCTGGCACTGGCACTGGCACTGTTATTGGTACTGGT
ACTGGCACCAGTGCTGGCACTGCCACTCTCTTTGGGCTTTAGCTTCTGCTCCCGCCTGGATCCGGGCTT
TGGCCCCAGGGTCCGATATCAGCTTCGTCCCAGTTGCAGGGCCCGAGCCATTCTCCAAATCCGCTTCCAT
CGCCTCTCAGTAC

11734.2contig

GCCAAGAAAGCCCGAAAGGTGAAGCATCTGGATGGGGAAGAGGATGGCAGCAGTGATCAGAGTCAGGCTTCTGG
AACCACAGGTGGCCGAAGGGTCTCAAAGGCCCTAATGGCCCCAATGGCCCGCAGGGCTTCAAGGGGTCCCATAG
CCTTTTGGGCCCGCAGGGCATCAAGGACTCGGTTGGCTGCTTGGGCCCGGAGAGCCTTGCTCTCCCTGAGATCA
CCTAAAGCCCGTAGGGGCAAGGCTCGCCGTAGAGCTGCCAAGCTCCAGTCATCCCAAGAGCCTGAAGCACCACC
ACCTCGGGATGTGGCCCTTTTGCAAGGGAGGGCAAATGATTTGGTGAAGTACCTTTTTGGCTAAAGACCAGACGA
AGATTCCCATCAAGCGCTCGGACATGCTGAAGGACATCATCAAAGAATACACTGATGTGTACCCCGAAATCATT
GAACGAGCAGGCTATTCCTTGGAGAAGGTATTTGGGATTCAATTGAAGGAAATTGATAAGAATGACCACTTGTA
CATTCTTCTCAGC

11736.1conta

3/101 11736.2contig

AAGCGGAAATGAGAAAGGAGGGAAAATCATGTGGTATTGAGCGGAAAACTGCTGGATGACAGGGCTCAGTCCTG
TTGGAGAACTCTGGGTGGTGCTGTAGAACAGGGCCACTCACAGTGGGGTGCACAGACCAGCACGGCTCTGTGAC
CTGTTTGTTACAGGTCCATGATGAGGTAAACAATACACTGAGTATAAGGGTTTGGTTTAGAAACTCTTACAGCAA
TTTGACAAAGTAATCTTCTGTGCAGTGAATCTAAGAAAAAAATTGGGGCTGTATTTGTATGTTCCTTTTTTTCA
TTTCATGTTCTGAGTTACCTATTTTTATTGCATTTTACAAAAGCATCCTTCCATGAAGGACCAGGAAGTTAAAAA
CAAAGCAGGTCCTTTATCACAGCACTGTCGTAGAACACAGTTCAGAGTTATCACCCCAAGGAGCCAGGGAGCTG
GGCTAAACCAAAGAATTTTGCTTTTGGTTAATCATCAGGTACTTGAGTTGGAATTGTTTTAATCCCATCATTAC
CAGGCTGGAXGTG

11739-1&2

11740.1.contig

4/101 11766.1.contig

11766.2.contig

11773.2.contig

11775-182

5/101 11777.1&2.cons

11779.2.contig

11781 & 37.cons

6/101 11781-76-87-37

11784-1 & 2

11785.2.contig

7/101 11718-1&2 cons

13690.4

13693.1

13694.1

8/101

13694.2

GACTGTCCTGAACAAGGGACCTCTGACCAGAGAGCTGCAGGAGATGCAGAGTGGCAGGAGTGGAAGCCAAA GAACACCCACCTTCCTCCCTTGAAGGAGTAGAGCCAACCACCTCAGAAGATACCTGTTTTATTGCTCTGGTCAAACAA GTCTTCCTGAGTTGACAAAAACCTCAGGCTCTGGTGACTTCTGAATCTGCAGTCCACTTTCCATAAGTTCTTGTG CAGACAACTGTTCTTTTGCTTCCATAGCAGCAACAGATGCTTTTGGGGCTAAAAGGCATGTCCTCTGACCTTGCA GGTGGTGGATTTTGCTCTTTTACAACATGTACATCCTTACTGGGCTGTGCTGTCACAGGGATGTCCTTGCTGGA CTGTTCTGCTATGGGGATATCTTCGTTGGACTGTTCTTCATGCTTAATTGCAGTATTAGCATCCACATCAGACA GCCTGGTATAACCAGAGTTTGGTGGTTACTGATTGTAGCTCCTTTTTTCCCACTTCATATGGCACAAGTATTTTTC CTCAACATCCTGGCTCTGGGAAG

13695.1

GAAATGTATATTTAATCATTCTCTTGAACGATCAGAACTCTRAAATCAGTTTTCTATAACARCATGTAATACAG
TCACCGTGGCTCCAAGGTCCAGGAAGGCAGTGGTTAACACACATGAAGAGTGTGGGAAGGGGGCTGGAAACAAAGT
ATTCTTTTCCTTCAAAGCTTCATTCCTCAAGGCCTCAATTCAAGCAGTCATTGTCCTTGCTTTCAAAAGTCTGT
GTGTGCTTCATGGAAGGTATATGTTTGTTGCCTTAATTTGAATTGTGGCCAGGAAGGGTCTGGAGATCTAAATT
CAGAGTAAGAAACCTGAGCTAGAACTCAGGCATTTCTCTTACAGAACTTGGCTTGCAGGGTAGAATGAANGGA
AAGAAACTTAGAAGCTCAACAAGCTGAAGATAATCCCATCAGGCATTTCCCATAGGCCTTGCAACTCTGTTCAC
TGAGAGATGTTATCCTG

13695.2

13697.1

TAGCTGTCTTCCTCACTCTTATGGCAATGACCCCATATCTTAATGGATTAAGATAATGAAAGTGTATTTCTTAC ACTCTGTATCTATCACCAGAAGCTGAGGTGATAGCCCGCTTGTCATTGTCATCCATATTCTGGGACTCAGGCGG GAACTTTCTGGAATATTGCCAGGGGGCATGGCAGGGGGCACAGTGCATTCTGGGGAATGCACATTGGCTCAG CCTGGGTAATGAGTGATATACATTACCTCTGTTCACAACTCATTGCCCAGCACCCAGTCACAAGGCCCCACCAAA TACCAGAGCCCCAAGAATGTAGTCCTGTTGATATGGTTTTGCTGTGTCCCAACCCAAATCTCATCTTGAATTGT AAGCTCCCATAATTCCCATGTGTTGTGGGAGGGACCTGGTG

9/101 13697.2

13699.1&2

13703.3

13705.1

10/101

13705.2

13707.4

13708.1&2

GGCGGGTAGGCATGGAACTGAGAAGAACGAAGAAGCTTTCAGACTACGTGGGGAAGAATGAAAAAACCAAAATT
ATCGCCAAGATTCAGCAAAGGGGACCAGGGGAGCTCCAGCCCGAGAGCCTATTATTAGCAGTGAGGAGCAGAAGCA
GCTGATGCTGTACTATCACAGAAGACAAGAGGAGCTCAAGAGATTGGAAGAAAATGATGATGATGATGCCTATTTAA
ACTCACCATGGGCGGATAACACTGCTTTGAAAAGACATTTTCATGGAGTGAAAGACATAAAGTGGAGACCAAGA
TGAAGTTCACCAGCTGATGACACTTCCAAAGAGATTAGCTCACCT

13709.1

11/101 13709.2

TATGAAGAAGGGAAAAGAAGATAATTTGTGAAAAGAAATGGGTCCAGTTACTAGTCTTTGAAAAAGGGTCAGTCTG
TAGCTCTTCTTAATGAGAATAGGCAGCTTTCAGTTGCTCAGGGTCAGATTTCCTTAGTGGTGTATCTAATCACA
GGAAACATCTGTGGTTCCCTCCAGTCTCTTTCTGGGGGGACTTGGGCCCACTTCTCATTTCATTTAATTAGAGGA
AATAGAACTCAAAGTACAATTTACTGTTGTTTAACAATGCCACAAAGACATGGTTGGGAGCTATTTCTTGATTT
GTGTAAAATGCTGTTTTTGTGTGCTCATAATGGTTCCAAAAATTGGGTGCTGGCCAAAGAGAGATACTGTTACA
GAAGCCAGCAAGAAGACCTCTGTTCATTCACACCCCCCGGGGATATCAGGAATTGACTCCAGTGTGTGCAAATCC
AGTTTGGCCTATCTTCT

13712.1&2

13714.1&2

13716.182

12/101 13718.2

13722.3

CATGCGTTTCACCACTGTTGGCCAGGCTGGTCTCGAACTCCTGGCCTCAAGCAATCCACCCGCCTCAGCCTCCA
AAAGTGCTGGGATTACAGATGTGAGCCATGGCACCATGCCAAAAGGCTATATTCCTGGCTCTGTGTTTCCGAGA
CTGCTTTTAATCCCAACTTCTCTACATTTAGATTAAAAAAATATTTTATTCATGGTCAATCTGGAACATAATTAC
TGCATCTTAAGTTTCCACTGATGTATATAGAAGGCTAAAGGCACAATTTTTATCAAATCTAGTAGAGTAACCAA
ACATAAAATCATTAATTACTTTCAACTTAATAACTAATTGACATTCCTCAAAAGAGCTGTTTTCAATCCTGATA
GGTTCTTTATTTTTTCAAAATATATTTGCCATGGGATGCTAATTTGCAATAAGGCGCATAATGAGAATACCCCA
AACTGGA

13722.4

13724-13698-13748

13/101

13730.1

13732.1

ATGGATCTTACTTTGCCACCCAGGTTGGAGTGCAGTGCTGCAATCTTGGCTCACTGCAGCCTTAACCTCCCAGG CTCAAGCTATCCTCCTGCCAAAGCCTTCCACATAGCTGGGACTACAGGTACACNGCCACCCACACCCCAGCTAAAA TTTTTGTATTTTTTGTAGAGACGGGATCTCGCCACGTTGCCCAGGCTGGTCCCATCCTGACCTCAAGCAGATCT GCCCACCTCAGCCCCCCAACGTGCTAGGATTACAGGCGTGAGCCACCGCACCCAGCCTTTGTTTTGCTTTTAAT GGAATCACCAGTTCCCCTCCGTGTCTCAGCAGCAGCTGTGAGAAATGCTTTGCATCTGTGACCTTTATGAAGGG GAACTTCCATGCTGAATGAGGGTAGGATTACATGCTCCTGTTTCCCGGGGGTCAAGAAAGCCTCAGACTCCAGC ATGATAAGCAGGGTGAG

13732.2

14/101 13735.1

13735.2

13736.1

13737,182

15/101 13738.1

TTTGACTTTAGTAGGGGTCTGAACTATTTATTTTACTTTGCCMGTAATATTTARACCYTATATATCTTTCATTA
TGCCATCTTATCTTCTAATGBCAAGGGAACAGWTGCTAAMCTGGCTTCTGCATTWATCACATTAAAAATGGCTT
TCTTGGAAAATCTTCTTGATATGAATAAAGGATCTTTTAVAGCCATCATTTAAAGCMGGNTTCTCCCAACACG
AGTCTGCTSASGGGGGKGAGCTGTGAACTCTGGCTGAAGGCTTTCCCATACACACTGCAATGACMTGGTTTCT
GACCAGBGTGAGTTA

13738.2

13739.1&2

GAGACAGGGTCTCACTTTGTCACCCAGGCTGGAATGCAGTGGTGCGATCTTACGTAGCTCACTGCAGCCCTGAC
CTCCTGGACTCAAACAATTCTCCTGCCTCAGCCCTGCAAGTAGCTGGGACTGTGGGTGCATGCCACCCATGCCTG
GCTAACTTTTGTAGTTTTTGTAAAGATGGGGTTTTGCCATGTTGCACATGCTGGTCTTGAACTCCTGAGCTCAA
ACGATCTGCCCACCTCGGCCTCCCAGAATGTTGGGATTACAGGGGTAAACCACCACCACGCCTGGCCCCATTAGGGT
ATTCTTAGCATCCACTTGCTCACTGAGATTAATCATAAGAAGATGATAAGCACTGGAAGAAAAAAATTTTTACTA
GGCTTTGGATATTTTTTTCCTTTTTCAGCTTTATACAGAGGATTGGATCTTTAGTTTTCCTTTTAACTGATAATA
AAACATTGAAAGGAAATAAGTTTACCTGAGATTCACAGAGATAACCGGCATCACTCCCTTGCTCAATTCCAGTC
TTTACCACATCAATTATTTTCAGAGGTGCAGGATAAAGGCCTTTTAGTCTGCTTTCGCACTTT
TTTGTAAACCTGTTGCCTGACAAATGGAATTGACAGCGTATGCCATGACTATTCCATTTTTCCACCTG
TCAATTTTTCCACCAATCCCTTGTCTCTCTTTTGGAGAGATCTTCTTATCAGCTAGTCCTTTTGGCAAAAGTAATT
GCAACTTCTTCTAGGTATTCTATTGTCCGTTCCACTGGTGGAACCCCTGGGACCAGGACTAAAACCTCCAG

13741.1

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14351.1

ACTCTGTCGCCCAGGCTGGAGCCCABTGGMGCGATCTCGACTCCCTGCAAGCTMCGCCTCACAGGWTCATGCCA
TTCTCCTGCCTCAGCATCTGGAGTAGCTGGGACTACAGGCGCCACCATGCCCAGCTAATTTTT

14351.2

ACCTTAAAGACATAGGAGAATTTATACTGGGAGAGAAAGCTTACAAATGTAAGGTTTCTGACAAGACTTGGGAG TGATTCACACCTGGAACAACATACTGGACTTCACACTGGABAGAAACCTTACAAGTGTAATGAGTGTGGCAAAG CCTTTGGCAAGCAGTCAACACTTATTCACCATCAGGCAATTCA

14354.2

AGTCAGGATCATGATGGCTCAGTTTCCCACAGCGATGAATGGAGGGCCAAATATGTGGGCTATTACATCTGAAG
AACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGGAGGTTACATAACAGGTGATCAAGCCCGT
ACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAATATGGGCCTTATCAGATCTGAACAAGGA
TGGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATCAAGTTAAAGTTGCAGGGCCAACAGCTGC
CTGTAGTCCTCCCTCCTATCATGAAACAACCCCCTATGTTCTCTCCACTAATCTCTGCTCGTTTTTGGGATGGGA
AGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCACCTATAGCAACACCCCTTGTCTTCTGCTAC
TTCAGGGACCAGTATTCCTCCCTAATGATGCCTGCT

14354.1

17/101 16431.1.2

GTGGAGGTGAAACGGAGGCAAGAAAGGGGGCTACCTCAGGAGCGAGGGACAAAGGGGGCGTGAGGCACCTAGGC
CGCGGCACCCCGGCGACAGGAAGCCGTCCTGAACCGGGCTACCGGGTAGGGGAAGGGCCCGCGTAGTCCTCGCA
GGGCCCCAGAGCTGGAGTCGGCTCCACAGCCCCGGGCCGTCGGCTTCTCACTTCCTGGACCTCCCCGGCGCCCCG
GGCCTGAGGACTGGCTCGGCGGAGGAGAAGAGGAAACAGACTTGAGCAGCTCCCCGTTGTCTCGCAACTCCAC
TGCCGAGGAACTCTCATTTCTTCCCTCGCTCCTTCACCCCCCCACCTCATGTAGAAAAGGTGCTGAAGCGTCCGGA
GGGAAGAAGAACCTGGGGCTACCGTCCTGGCCTTCCCMCCCCCTTCCCGGGGCGCTTTTGTGGGGCGTGGAGTTGG
GGTTGGGGGGTGGGTGGGGGTTCTTTTTTTGGAGTGCTGGGGAACTTTTTTTCCCTTCTTCAGGTCAGGCGAAAG
GGAATGCCCAATTCAGAGAGACATGGGGGCAAGAAGGACGGGAACTGGAGGAGCTTCTGGAACTTTTGCAGCCGTC
ATCGGGAGGCGGCAGCTCTAACAGCAGAAGAAGGACGGGAGTGGAGGAGCTTCTGGAACTTTTGCAGCCGTC
ACCCCAAAGACATGGGGTTGGTGACCCCCGAAGCAGCACCTCCCTGGGCACAACCAAACCATTACAAACCTTTTGGTGGAGCTAT
GATGATATCAGCTCTGATTCCGACACCTTCTCCCGATGACATCGTCACCACCACCAGCAGCAGCGTTCCCGGGACTTAC
TAAAAGCTAAACAGACCG

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16432-2

17184.3

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CAAGCGTTCCTTTATGGATGTAAATTCAAACAGTCATGCTGAGCCATCCCGGGCTGACAGTCACGTTWAAGACA CTAGGTCGGGCGCCACAGTGCCACCCAAGGAGAAGAAGAATTTTGGAATTTTTCCATGAAGATGTACGGAAATCT GATGTTGAATATGAAAATGGCCCCCCAAATGGAATTCCAAAAGGTTACCACAGGGGCTGTAAGACCTAGTGACCC TCCTAAGTGGGAAAGAGGAATGGAGAATATTTCTGATGCATCAAGAACATCAGAATATAAAACTGAGATCA TAATGAAGGAAAATTCCATATCCAATATGAGTTTACTCAGAGACAGTAGAAACTATTCCCAGG

17185.1

TAGGAATAACAAATGTTTATTCAGAAATGGATAAGTAATACATAATCACCCTTCATCTCTTAATGCCCCTTCCT
CTCCTTCTGCACAGGAGACACAGATGGGTAACATAGAGGCATGGGAAGTGGAGGAGGACACAGGACTAGCCCAC
CACCTTCTCTCCCGGTCTCCCAAGATGACTGCTTATAGAGTGGAGGAGGCAAACAGGTCCCCTCAATGTACCA
GATGGTCACCTATAGCACCAGCTCCAGATGGCCACGTGGTTGCAGCTGGACTCAATGAAACTCTGTGACAACCA
GAAGATACCTGCTTTGGGATGAGAGGGAGGATAAAGCCATGCAGGGAGGATATTTACCATCCCTACCCTAAGCA
CAGTGCAAGCAGTGAGCCCCCGGCTCCCAGTACCTGAAAAAACCAAGGCCTACTGNCTTTTGGATGCTCTCTTGG
GCCACG

17188.2

17190.1

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AGCCAGATGGCTGAGAGCTGCAAGAAGAAGTCAGGATCATGATGGCTCAGTTTCCCACAGCGATGAATGGAGGG CCAAATATGTGGGCTATTACATCTGAAGAACGTACTAAGCATGATAAACAGTTTGATAACCTCAAACCTTCAGG AGGTTACATAACAGGTGATCAAGCCCGTACTTTTTTCCTACAGTCAGGTCTGCCGGCCCCGGTTTTAGCTGAAA TATGGGCCTTATCAGATCTGAACAAGGATGGAAGATGGACCAGCAAGAGTTCTCTATAGCTATGAAACTCATC ACTAATCTCTGCTCGTTTTTGGGATGGGAAGCATGCCCAATCTGTCCATTCATCAGCCATTGCCTCCAGTTGCAC CTATAGCAACACCCTTGTCTTCTGCTACTTCAGGGACCAGTATTCCTCCCCTAATGATGCCTGCTCCCCTAGTG CCTTCTGTTAGTACATCCTCATTACCAAATGGAACTGCCAGTCTCATTCAGCCTTTATCCATTCCTTATTCTTC TTCAACATTGCCTCATGCATCATCTTACAGCCTGATGATGGGGAGGATTTGGTGGTGCTAGTATCCAGAAGGCCC AGTCTCTGATTGATTTAGGATCTAGTAGCTCAACTTCCTCAACTGCTTCCCTCTCAGGGAACTCACCTAAGACA GGGACCTCAGAGTGGGCAGTTCCTCAGCCTTCAAGATTAAAGTATCGGCAAAAATTTAATAGTCTAGACAAAGG CTACTATTTGGACTCTGGCTGACATCGATGGTGACGGACAGTTGAAAGCTGAAGAATTTATTCTGGCGATGCAC CTCACTGACATGGCCAAAGCTGGACAGCCACTACCACTGACGTTGCCTCCCGAGCTTGTCCCTCCATCTTTCAG AGGGGGAAAGCAAGTTGATTCTGTTAATGGAACTCTGCCTTCATATCAGAAAACACAAGAAGAAGAAGACCCTCAGA AGAAACTGCCAGTTACTTTTGAGGACAAACGGAAAGCCAACTATGAACGAGGAAACATGGAGCTGGAGAAGCGA GAAACAGAGAGAACTGCAAGAGCAAGAATGGAAGAAGCAGCTGGAGTTGGAGAAACGCTTGGAGAAACAGAGAG AGCTGGAGAGACAGCGGGAGGAAGAGAGAGAGAAAAGGAGATAGAAAGACGAGAGGCAGCAAAACAGGAGCTTGAG CATTGTCAGGCTGAGCTCCAGAAAGAAAAGTCTCCACCTGGAACTGGAAGCAGTGAATGGAAAACATCAGCAGA TCTCAGGCAGACTACAAGATGTCCAAATCAGAAAGCAAACACAAAAGACTGAGCTAGAAGTTTTGGATAAACAG GGTCCCTGAGAAGCAGCTATTAAACGAAAGAATTAAAAACATGCAGCTCAGTAACACACCTGATTCAGGGATCA GTTTACTTCATAAAAAGTCATCAGAAAAGGAAGAATTATGCCAAAGACTTAAAGAACAATTAGATGCTCTTGAA AAAGAAACTGCATCTAAGCTCTCAGAAATGGATTCATTTAACAATCAGCTGAAGGAACTCAGAGAAAGCTATAA TAGAGCAAAAAAAAAAAA

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Fig. 7A

AGCGTGGTCGCGGCCGAGGTCCAGTCGCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGGAAGATCTCTGCTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACATCATAGCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGCTCGA

Fig. 7B

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Probe 2	7	270A Liver N	SS6 Springl Cor	SQ1: Feral tissue	415A April N	873 Breisin	II Celon N	IZ Sken N	292A Dendritte	S2 Panemens N	840 PBMC cuct	CT10 Small inte	CTS Heart N	S7 Overy N	243A Esophago	S10 Skelenim	SZI Oraty N	C'10 Kithrey N	GARS COTT S.P. CS.	334A Large Inhast	C74 Bone Marroy	3643 Overy'N	Crist Brain X	CTI2 Ling N	S6 Stomach N
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+16.7	26A Ovary T (metr R		j d	115A Anta'N	422X0611	202	462	46.3	73	3.5	13	
+10.7 2	15.4 Ovury T	The second secon		270 Liver N	42200606	16101	Š	61:2	₹,	œ.	4	•
6.64	85A Overy T			591 Fetal degue	42axo60n	100	3	2	*	77	20	
- SS - SS -	23 Overy F		,	SS6 Spinal Cord N	142200628	1381	88	7.3	E.	4	73	
+6.4 3	83A Ovary T (mote 19)		Į	Colon	422BD609	4807	748	27.6	ŧ	22	47	
	263A Ovary T			S73 Breast N	422H0623	9815	509	<u>.</u>	*	4	74	
-	429A Ovary T (men is			MAA Ovary N	42210614	2661	543	20.3	3	6.7.	.6 .	
•	64A Ovary T			S2 Pancreas N	422ND629	7934	22.74	38.8	7	æ	71.	
29	S25 Ovnry T	The state of the s		T4 Bone Marrow	7 422H0619	480	1375	3.5	8	3:0	æ	
+28	26IA Ovary T			S 10 Skeletal musc	142230621	8008	324	34.6	3	7	3	
12.5	SI 15 Overy T (mets 13	Treatment of the last		T10 Small intesti	n422C0604	1868 1868 1878	738	م مور	8	22	15	
+23	9334 Overy T (SCIL	The state of the s	7	2 Skin N	422R0601	2552	11.13	12.7	4	520	7	-
23	S22 Overy T		_	TO Kidney N	42290627	386	8	35	3	4	69	
+2.2	384A Overy Trinets by			72A Dendritic cel	M2240608	3516	1567	18.7	33	976	ve.	
2.0	382A Overv.T			Number of the	42200610	86	1520	C)	.9	Č	9	
61+	265A Overry E.			IS Hear	42200624	2063	1080	35 26	&	33	81	
7	265A Ovary T	THE VIEW OF THE PARTY OF THE PA	Y	27. Ovary N	42250603	1550	8,47	7.0	æ 28	: :	58	
+	262A Ovary T		.01	134 Large Intesti	r422A0622	SS SS	1631	725	52	et m	77	
7	386A, Ovary T		1 21	S40 PBMC (acrive	142210605	33	738	a'e	얺	77	ឧ	
**	88A Ovary T			TI2 Lung N	422V0625	863	67.1	5.3	B	3.1	9	•
7	335A Owary T			N COMPA IN	42220626	3	567	er.	Ŝ	77	9	
72.7			ę,	485 OT S-P (SCII	3422Y0602	4188	S	21.6	\$	S.	99	
7	128A Owary T (meta		3	43A Exphingus N	142240612	22	689	Ĵ.	3	ci co	ß.	
9	201A Overy T		<i>y</i> ,	6 Stomach N	422W0620	88	1018	7.4	8	32	ଷ	
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Probet	8/8	55.2	42.6	21.7	440	î		4 5 4 5	7	# : 2 :	29.1	38.	3.4	E.Z.	6.7	11.8	17.0	×	, c	11.2	50	i v	4	2 (7.5	2 6	i	
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Proble 2	Nema	Kry Acres N	337 Bullets	So spins con	ALC CERTS IN	191 Fetal tissue	73 Breast N	T4 Bone Mirri	70A Liver N	I Colon N	10 Skelem mo	N Panoritas N	Tito Resin N	A Clear N	COMMENTS.	Tio Small inc	N TOTAL CIT	72A Dominue	27 Overy'n	40 PEMC (BCD	134A Large Inte	CVary	TIT LINGN	of Stoutstern N	43A Esophague	485 OT 5-P (SC	To Kidney N	
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	HOT PERDE A	The state of the s	+332, 426A Ovary 1	+15.7-523 Overy 7	+126 429A Dyary 1	+80,385A Ovary	*7.1.2634 Orac	-5.8.525 Ovary T	15.0 205.4 Ovar	4.5 3834 Overv 1	14 2614 Overv	Ž	S	J		+2.5 \$1.15 Overy T	+2.4 265A Ovury	+2.3 384A Overy 1	+1.9 2664 Overy 7	-1.9 386A: Ovary 1	#1.7 262 A Overy	-L3 335A Overy	-1.1 288A Ovary	1-1.1 ZOLA COVARY I	+1.1 4284 Ovary 7	-1.0 9485 OT 1-P	\$22, Overy T	ı
`	ene.	Ame	(2/V0189 (DJ)	121Vd189 (D1)	12 (X0189 (D)1)	121.V0189 (DT)	(10) WIRG (DI)	12 INDING (D13		CLUMB TOUR	150 (01) (01)	Tro Agrica	42 VOIS9 [191]	121-V0189 (EU.)	421V0189 (D13	(21V0189 (DI)	(21V0189 (D1)	(21V0189 (D1)		421V0189 (DJ)		121V0189 (D1)		101 VA 180 (D) 13	C) VAISO (D) 1			,

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Probet	Value	\$41	2318	1252	9507	5456	3	305	3733	+163	1565	3435	2867	297	410	2291	1892	200	252	382	558	2582	22,61	1739
iEid	9	22X0611	2200628	2210614	22X0607	2200606	42200624	2200610	2230621	22H0623	2200604	22N0629	12240608	2290627	2210605	422R0601	22A0622	22/0/25	2240612	2220626	22W0620	22Y0602	22B0609	2250603
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Probe 2	Name	15A Agn	56 Spinal	SA O	9) Fetal	70A.Liver	TS Hear N	TIP Brain N	10 Skelet	73 Breast	TIO Smal	2 Plancing	74 Dend	TO Kidne	40 PHMC	Skin Z	34A Larm	TI2 LINE N	134 Esop	7 Overy	Stornac	185 OT 5-	Colon	37 Owary]
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		87 (E11)	87 (1111)	87 (011)	87 (Et1)	187 (EII)	87 (E11)	87 (111)	87 (HII)	87 (TE11)	8年	87:(EL!)	D. HELLIN	FIETT	7 (EII)	7 (BIL)	-	37 [四1]	==	7 (E11)	11111 2	(7 (E)1)	T(B)	7 (B(1)
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35/101

11721-1

11721-2

11724-1

11724-2

36/101 11725-32-1.2

11726-182

11727-1&2

37/101 11728.1.40.19.19

11728.2.40.19.19

CCCGTGGGTGCCATCCACGGAGTTGTTACCTGATCTTTGGAAGCAGGATCGCCCGTCTGCACTGCAGTGGAAGC
CCCGTGGGCAGCAGTGATGGCCATCCCCGCATGCCACGGCCTCTGGGAAGGGGCAGCAACTGGAAGTCCCTGAG
ACGGTAAAGATGCAGGAGTGGCCGGCAGAGCAGTGGGCATCAACCTGGCAGGGGCCACCCAGATGCCTGCTCAG
TGTTGTGGGCCATTTGTCCAGAAGGGGACCGCAGCAGCTGTAGCTGGCTCCTCCGGGGTCCAGGCAGCAGCCA
CAGGGCAGAACTGACCATCTGGGCACCGCGTTCCAGCCACCAGCCCTGCTGTTAAGGCCACCCAGCTCACCAGG
GTCCACATGGTCTGCCTGCGTCCGACTCCGCGGTCCTTGGGCCCTGATGGTTCTACCTGCTGTGAGCTGCCCAG
TGGGAAGTATGGCTGCCCAATGCCCAACGCCACCTGCTGCTCCGATCACCTGCACTGCCCCAAGACACT
GTGTGTGACCTGATCCAGAGTAAGTGCCTCCCCAAGGAGAACG

11730-1

11730-2

Fig. 15C

38/101

11732.1contig

11732.2contig

11735-1-2

11740.2.contig

39/101 11765.2&64.2.contig

CGCCTCCACCATGTCCATCAGGGTGACCCAGAAGTCCTACAAGGTGTCCACCTCTGGCCCCCGGGCCTTCAGCA
GCCGCTCCTACACGAGTGGGCCCGGTTCCCGCATCAGCTCCTCGAGCTTCTCCCGAGTGGGCAGCAACTTT
CGCGGTGGCCTGGGCGGCGGCTATGGTGGGGCCAGCGCATCACCGCAGTTACCGCAGTTACGGTCAACCAGAG
CCTGCTGAGCCCCCTTGTCCTGGAGGTGGACCCCAACATCCAGGCCGTGCGCACCCCAGGAGAAGAGGAGCAGATCA
AGACCCTCAACAACAAGTTTGCCTCCTTCATAGACAAGGTACGGTTCCTGGAGCAGCAGCAGAACAAGATGCTGGAG
ACCAAGTGGAGCCTCCTGCAGCAGCAGAAGACGGCTCGAAGCAACATGGACAACATGTTCGAGAGCTACATCAA
CARCCTTAGGCGGCAGCTGGAGACTCTGGGCCAGGAGAAGATGAGATCAATAAGCGTACAGAGAGCTTGCAACATGCAGG
GGCTGGTGGAGGACTTCAAGAACAAGTATGAGGATGAGATCAATAAGCGTACAGAGATCTGGCAACCATGCAGA
CCAAGATCAACTTCCTCAGGACAACAAGCTTACATGAACAAGGTAGAGCTGGAGTCCCAGATCTCGGACACATCTG
TCGTGCTGTCCATGGACAACAGCCGCTCCCTGGACATGGACAGCATCATTGCTGAGGTCAAGTCTCGGACACATCTG
GATATTGCCAACCGCAGCCGGGCTGAAGGCTGAGACATGTACCAGGTCAAGTATGAGGAGCTGCAGACCTGGC
TGGGAAGCACCGGGGCTGAAGGCTGAGACATGTACCAGGTCAAGTATGAGGAGCTGCAGACCTGGC
TGGGAAGCACCGGGGCTGAAGGCCACAAAGACTGAGATCTCTGAGATGAACCCGGAACATCAGCCCGGCT
XCAGGCTGAGATTGAGGGCCTCAAAGGCCAGAXGGCTTXCCTGGAXGXCCGCCAT

11767.2.contig

CCCGGAGCCAGCGACGAGGGAAAATGGCAGACAATTTTTCGCTCCATGATGCGTTATCTGGGTCTGGAAACCCAAACCCTCAAGGATGGCCTGGCGCATGGGGGAACCAGCCTGCTGGGGCAGGGGCTACCCAGGGGCTTCCTATCCTGGGGCCTACCCCGGGCACCCCCAGGGGCTTATCCTGGACAGCCCCTACCCTGGAGCACCTGCACCTGCACCTGCAGCCTTATCCCGGAGCCCCTACCCAGGGCCCTACCCCATCCTGGAGCCTTATCCCGGAGCACCTGCACCTGCACCTGCACCCAGGGCCACCCAGCGGCCCCTGGGGCCACCCATCCCATCCTGGACAGCCCAAGTGCCACCGGAGCCTACCCCTGCCACTGCCCCTATGGCGCCCCTGCTGGGCCACTGATTGTGCCTTTATAACCTGCCTTTTGCCTGGGGGAGTGGTGCCTCGCATGCTGATAACAATTCTGGGCACCGCTTCAATGAACAACAGAACAGAACAGAACTTGCTTTAGATTTCCAAAGAGGGAAATGATGTTGCCTTCCACTTTAACCCACGCTTCAATGAGAACAACAGGAGAGTCATTGGTTGCAATACAAAGCTGGATAA

11768-1&2

GGGAATGCAACACTTTATTGAAAGGAAAGTGCAATGAAATTTGTTGAAACCTTAAAAGGGGAAACTTAGACAC CCCCCCTCRAGCGMAGKACCARGTGCARAGGTGGACTCTTTCTGGATGTTGTAGTCAGACAGGGTRCGWCCATC TTCCAGCTGTTTYCCRGCAAAGATCAACCTCTGCTGATCAGGAGGRATGCCTTCCTTATCTTGGATCTTTGCCT TGACATTCTCGATGGTGTCACTGGGCTCCACCTCGAGGGTGATGGTCTTACCAGGTCAGGGTCTTCACGAAGATY TGCATCCCACCTCTGAGACGGAGCACCAGGTGCAGGGTRGACTCTTTCTGGATGTTGTAGTCAGACAGGGTGCG YCCATCTTCCAGCTGCTTTCCSaGCAAAGATCAACCTCTGCTGGTCAGGAGGRATGCCTTCCTTGTCYTGGATC TTTGCYTTGACRTTCTCAATGGTGTCACTCGGCTCCACTTCGAGAGTGATGGTCTTACCAGTCAGGGTCTTCAC GAAGATCTGCATCCCACCTCTAAGACGGAGCACCAGGTGCAGGGTGGACTCTTTCTGGATGGTTTTCCAGACACAAGATCAACCT

40/101 11768-1&2-11735-1**&**2

11769.1.contig

11769.2.contig

AGCGCGGTCTTCCGGCGCGAGAAAGCTGAAGGTGATGTGGCCGCCCTCAACCGACGCATCCAGCTCGTTGAGGA
GGAGTTGGACAGGGCTCAGGAACGACTGGCCACGGCCCTGCAGAAGCTGGAGGAGAAAAAGCTGCAGATG
AGAGTGAGAGAGGAATGAAGGTGATAGAAAACCGGGCCATGAAGGATGAGGAGAAGATGAGGAGATTCAGGAGATG
CAGCTCAAAGAGGCCAAGCACATTGCGGAAGAGGCTGACCGCAAATACGAGGAGGAGATGCTCGTAAGCTGGTCAT
CCTGGAGGGTGAGCTGGAGAGGGCAGAGGAGGCTGCGGAGGTGTCTGAACTAAAATGTGGTGACCTGGAAGAAG
AACTCAAGAATGTTACTAACAATCTGAAATCTCTGGAGGCTGCATCTGAAAAGTATTCTGAAAAGGAGGACAAA
TATGAAGAAGAAATTAAACTTCTGTCTGACAAACTGAAAAGGAGGCTGAGACCCGTGCTGAATTTGCAGAGAGAAAC
GGTTGCAAAACTGGAAAAGACAATTGATGACCTGGAAGAGAAACTTGCCCCAGC

11770.1.contia

41/101 11770.2.contig

11773.1.contig

11778.1.contig

11778-2&30-2

42/101

11782.1.contig

ATCTACGTCATCAATCAGGCTGGAGACACCATGTTCAATCGAGCTAAGCTGCTCAATATTGGCTTTCAAGAGGC
CTTGAAGGACTATGATTACAACTGCTTTGTGTTCAGTGATGTGGACCTCATTCCGATGGACGACCGTAATGCCT
ACAGGTGTTTTTCGCAGCCACGGCACATTTCTGTTGCAATGGACAAGTTCGGGTTTAGCCTGCCATATGTTCAG
TATTTTGGAGGTGTCTCTGCTCTCAGTAAACAACAGTTTCTTGCCATCAATGGATTCCCTAATAATTATTGGGG
TTGGGGAGGAGAAGATGACGACATTTTTAACAGATTAGTTCATAAAGGCATGTCTATATCACGTCCAAATGCTG
TAGTAGGGAGGTGTCGAATGATCCGGCATTCAAGAGACAAAAAATGAGCCCCAATCCTCAGAGGTTTGACCGG
ATCGCACATACAAAGGAAACGATGCGCTTCGATGGTTTGAACTCACTTACCTACAAGGTGTTGGATGTCAGAGA
TACCCGTTATATACCCAAATCAC

11782.2. contig

11783-1 & 2

11786.1.contig

GCTCTTCACACTTTTATTGTTAATTCTCTTCACATGGCAGATACAGAGCTGTCGTCTTGAAGACCACCACTGAC CAGGAAATGCCACTTTTACAAAATCATCCCCCCTTTTCATGATTGGAACAGTTTTCCTGACCGTCTGGGAGCGT TGAAGGGTGACCAGCACATTTGCACATGCAAAAAAGGAGTGACCCCAAGGCCTCAACCACACTTCCCAGAGCTC ACCATGGGCTGCAGGTGACCTGCAGGTTTGCCAGGGTTCGTGAGGTTCCTTGCTGCTGCGGTGGGGAGGCCCTCA AGAACTGAGAGGCCGGGGTATGCTTCATGAGTTTAACATTTACGGGACAAAAGCGCATCATTAGGATAAGGAA CAGCCACAGCACTTCATGCTTGTGAGGGTTAGCTGTAGGAGCGGGTGAAAGGATTCCAGTTTATGAAAATTTAA AGCAAACAACGGTTTTTAGCTGGGGAAAACAGGGAAAACTGTGATGTCGGCCAATGACCACCATTTTTCTGCC CATGTGAAGGTCCCCATGAAACC

PCT/US01/22635

43/101 11786.2.contig

CAAGCGCTTGGCGTTTGGACCCAGTTCAGTGAGGTTCTTGGGTTTTGTGCCTTTGGGGATTTTGGTTTGACCCA
GGGGTCAGCCTTAGGAAGGTCTTCAGGAGGAGGCCGAGTTCCCCTTCAGTACCACCCCCTCTCCCCACTTTCC
CTCTCCCGGCAACATCTCTGGGAATCAACAGCATATTGACACGTTGGAGCCGAGCCTGAACATGCCCCTCGGCC
CCAGCACATGGAAAACCCCCTTCCTTGCCTAAGGTGTCTGAGTTTCTGGCTCTTGAGGCATTTCCAGACTTGAA
ATTCTCATCAGTCCATTGCTCTTTGAGTCTTTTGCAGAGAACCTCAGATCAGGTGCACCTGGGAGAAAGACTTTGT
CCCCACTTACAGATCTATCTCCTCCCTTGGGAAGGGCAGGGAATGGGGACCGTGTATGGAGGGGAAGGGATCTC
CTGCGCCCTTCATTGCCACACTTGGTGGGACCATGAACATCTTTAGTGTCTGAGCTTCTCAAATTACTGCAATA
GGA

13691.182

13692.1&2

13693.2

44/101 13696.1-13744.1

13700.1

CAAGGGATATATGTTGAGGGTACRGRGTGACACTGAACAGATCACAAAGCACGAGAAACATTAGTTCTCTCCCT
CCCCAGCGTCTCCTTCGTCTCCCTGGTTTTCCGATGTCCACAGAGTGAGATTGTCCCTAAGTAACTGCATGATC
AGAGTGCTGKCTTTATAAGACTCTTCATTCAGCGTATCCAATTCAGCAATTGCTTCATCAAATGCCGTTTTTGC
CAGGCTACAGGCCTTTTCAGGAGAGTTTAGAATCTCATAGTAAAAGACTGAGAAATTTAGTGCCAGACCAAGAC
GAATTGGGTGTAGGCTGCATTNCTTTCTTACTAATTTCAAATGCTTCCTGGTAAGCCTGCTGGGAGTTCGAC
ACAAGTGGTTTGTTTGTTGCTCCAGATGCCACTTCAGAAAGATACCTAAAATAATCTCCTTTTCATTTTCAAAGT
AGAACAC

13700.2

TCCGGAGCCGGGGTAGTCGCCGCCGCCGCCGCCGCTGCAGCCACTGCAGGCACCGCTGCCGCCGCCTGAGTAGT
GGGCTTAGGAAGGAAGAGGTCATCTCGCTCGGAGCTTCGCTCGGAAGGGTCTTTGTTCCCTGCAGCCCTCCCAC
GGGAATGACAATGGATAAAAGTGAGCTGGTACAGAAAGCCAAACTCGCTGAGCAGGCGGATATGATGATA
TGGCTGCAGCCATGAAGGCAGTCACAGAACAGGGGCATGAACTCTCCAACGAAGAGAGAAAATCTGCTCTCTGTT
GCCTACAAGAATGTGGTAAGGCCGCCCGCCGCTCTTCCTGGCGTGTCATCTCCAGCATTGAGCAGAAAACAGAG
AGGAATGAGAAGAAGCAGCAGATGGGCAAAGAGTACCGTGAGAAGATAGAGGCAGAACTGCAGGACATCTGCAA
TGATGTTCTGGAGCTTGTTGGACAAATATCTTATTCCAATGCTACACAACCCAGAAA

13701.1

45/101

13701.2

13702.2

AGCTGGCGCTAGGGCTCGGTTGTGAAATACAGCGTRGTCAGCCCTTGCGCTCAGTGTAGAAACCCACGCCTGTA AGGTCGGTCTTCGTCCATCTGCTTTTTTCTGAAATACACTAAGAGCAGCCACAAAACTGTAACCCTCAAGGAAAC CATAAAGCTTGGAGTGCCTTAATTTTTAACCAGTTTCCAATAAAACGGTTTACTACCT

13704.2-13740.2

GGAGATGAAGATGAGGAAGCTGAGTCAGCTACGGGCARGCGGGCAGCTGAAGATGATGAGGATGACGATGTCGA TACCAAGAAGCAGAAGACCGACGAGGATGACTAGACAGCAAAAAAGGAAAAGTTAAA

13706.1

GATGAAAATTAAATAATTAATTAATTAATCAAAAGGCACTACGATACCACCTAAAACCTACTGCCTCAGTGGCAGTA KGCTAAKGAAGATCAAGCTACAGSACATYATCTAATATGAATGTTAGCAATTACATAKCARGAAGCATGTTTGC TTTCCAGAAGACTATGGNACAATGGTCATTWGGGCCCAAGAGGATATTTGGCCNGGAAAGGATCAAGATAAAANGTAAAG

13706.2

46/101

13707.3

13710.2

13710-1

TGAGATTTATTGCATTTCATGCAGCTTGAAGTCCATGCAAAGGRGACTAGCACAGTTTTTAATGCATTTAAAAA ATAAAAGGGAGGTGGGCAGCAAACACACAAAGTCCTAGTTTCCTGGGTCCCTGGGAGAAAAGAGTGTGGCAATG AATCCACCCACTCTCCACAGGGAATAAATCTGTCTCTTAAATGCAAAGAATGTTTCCATGGCCTCTGGATGCAA ATACACAGAGCTCTGGGGTCAGAGCAAGGGATGGGGAGAGAGCCACGAGTGAAAAAGCAGCTACACACATTCAC CTAATTCCATCTGAGGGCAAGAACAACGTGGCAAGTCTTGGGGGTAGCAGCTGTT

13711.1

47/101 13711.2

13713.1&2

TCACTTTATTTTTCTTGTATAAAAACCCTATGTTGTAGCCACAGCTGGAGCCTGAGTCCGCTGCACGGAGACTC TGGTGTGGGTCTTGACGAGGTCGTCAGTGAACTCCTGATAGGGAGACTTTGGTGAATACAGTCTCCTTCCAGAGG TCGGGGGTCAGGTAGCTGTAGGTCTTAGAAATGGCATCAAAGGTGGCCTTGGCGAAGTTGCCCAGGGTGGCAGT GCAGCCCCGGGCTGAGGTGTAGCAGTCATCGATACCAGCCATCATGAG

13715.4

13717.1&2

48/101 13719.182

13721.1

13721.2

13723.1

CATGGGTTTCACCAGGTTGGCCAGGCTGCTCTTGAACTSCTGACCTCAGGTGATCCACCCGCCTCGGCCTCCCA
AAGTGCTGGGATTACAGGCGTGAGCCACCACGCCCGGCCCCCAAAGCTGTTTCTTTTTGTCTTTAGCGTAAAGCT
CTCCTGCCATGCAGTATCTACATAACTGACGTGACTGCCAGCAAGCTCAGTCACTCCGTGGTCTTTTTCTCTTT
CCAGTTCTTCTCTCTCTCTCAAGTTCTGCCTCAGTGAAAGCTGCAGGTCCCCAGTTAAGTGATCAGGTGAGGG
TTCTTTGAACCTGGTTCTATCAGTCGAATTAATCCTTCATGATGG

49/101

13723.2

13725.1

13725.2

13726.1&2

50/101 13727.1

13727.2

13728.1&2

13731.1&2

TGTGCCAGTCTACAGGCCTATCAGCAGCGACTCCTTCAGCAACAGATGGGGTCCCCTGTTCAGCCCAACCCCAT GAGCCCCAGCAGCAGCATATCAGCCCCAAATCAGGCCCAGCCCACACCCACACCCAACCCCACACCCAGCCAGCCCAGATCCCTAATTCTC TCTCCAATCAAGTGCGCTCTCCCCAGCCTGTCCCTTCTCCACGGCCACAGTCCCAGCCCCCCCACTCCAGTCCT TCCCCAAGGATGCAGCCTCAGCCTTCTCCACACCACGTTTCCCCACAGACAAGTTCCCCACATCCTGGACTGGT AGTTGCCCAGGCCAACCCCATGGAACAAGGGCATTTTGCCAGCC

51/101

13734.1&2

13736.2

13744.2-13696.2

13746.1&2-13720.1&2

52/101

14347.1

14347.2

CTCCTCTTGGTACATGAACCCAAGTTGAAAGTGGACTTAACAAAGTATCTGGAGAACCAAGCATTCTGCTTTGA
CTTTGCATTTGATGAAACAGCTTCGAATGAAGTTGTCTACAGGTTCACAGCAAGGCCACTGGTACAGACAATCT
TTGAAGGTGGAAAAGCAACTTGTTTTGCATATGGCCAGACAGGAAGTGGCAAGACACATACTATGGGCGGAGAC
CTCTCTGGGAAAGCCCAGAATGCATCCAAAGGGATCTATGCCATGGCCTTCCGGGACGTCTTCTTCTTCTGAAGAAT
CAACCCTGCTACCGGAAGTTGGGCCTGGAAGTCTATGTGACATTCTTCGAGATCTACAATGGGAAGCTGTTTGA
CCTGCTCAACAAGAAGGCCAAGCTTGCGCGTGCTGGAAGACGCCAAGCAACAGGTGCAAGTGGTGGGGGCTTGC
AGGAACATCTGGNTAACTCTGCTTGATGATGACANTCAAGATGATCGACATGGCAGCGCCTGCAGA

14348.2&14350.1&2

14349.182

TTCGTGAAGACCCTGACTGGTAAGACCATCACTCTCGAAGTGGAGCCCGAGTGACACCATTGAGAATGTCAAGG
CAAAGATCCAAGACAAGGAAGGCATCCCTCCTGACCAGCAKAGGTTGATCTTTGCTGGGAAACAGCTGGAAGAT
GGACGCACCCTGTCTGACTACAACATCCAGAAAGAGTCCACCCTGCACCTGGTGCTCCGTCTCAGAGGTGGGAT
GCAAATCTTCGTGAAGACCCTGACTGGTAAGACCATCACCCTCGAGGTGGAGCCCAGTGACACCATCGAGAATG
TCAAGGCAAAGATCCAAGATAAGGAAGGCATCCCTCCTGATCAGCAGAGGTTGATCTTTGCTGGGAAACAGCTG
GAAGATGGACGCACCCTGTCTGACTACAACATCCAGAAAGAGTCCACTCTGCACTTTGGTCCTGCGCTTGAGGGG
GGGTGTCTAAGTTTCCCCTTTTAAGGTTTCAACAAATTTCATTGCACTTTCCTTTCAATAAAGTTGTTGCATTC

53/101 14352.1&2

14353.1

14353.2

17182.1&2

54/101

17183.2

GGTTCACAGCACTGCTGCTTGTGTTGTCCCGCCCAGGAATTCCAGGCTCACAAGGCTATCTTAGCAGCTCGTTC
TCCGGTTTTTAGTGCCATGTTTGAACATGAAATGGAGGAGAGAGCAAAAAGAATCGAGTTGAAATCAATGATGTGG
AGCCTGAAGTTTTTAAGGAAATGATGTGCTTCATTTACACGGGGAAGGCTCCAAACCTCGACAAAATGGCTGAT
GATTTGCTGGCAGCTGCTGACAAGTATGCCCTGGAGCGCTTAAAGGTCATGTGTGAGGATGCCCTCTGCAGTAA
CCTGTCCGTGGAGAACGCTGCAGAAATTCTCATCCTGGCCGACCTCCACAGTGCAGATCAGTTGAAAACTCAGG
CAGTGGATTTCATCAACTATCATGCTTCGGATGTCTTGGAGACCTCTTGGG

17186.1&2

17187.1&2

17191.1&89.1

55/101 17192.1&2

17193

56/101 16443.1.edit

16443.2.edit

16444.2.edit

AGCGTGGTTNCGGCCGAGGTCCCAACCAAGGCTGCANCCTGGATGCCATCAAAGTCTTCTGCAACATGGAGACT GGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAGGA CAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGACC CTGCCGATGTGGACCTGCCCGGGCGGNCGCTCGA

16445.1.edit

AGCGTGGTCGCGGCCGAGGTCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATGTGCCACTCTGACTGGAA GAGTGGAGAGTACTGGATTGACCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGA CTGGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAAG GACAAGAGGCATGTCGGTTCGGCGAGAGACCTGACCGATGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGA CCCTGCCGATGTGGACCTGCCCGGGCCGCCGCTCGA

57/101 16445.2.edit

16446.1.edit

TCGAGCGCCCCGGGCAGGTCCTCCTCAGAGCGGTAGCTGTTCTTATTGCCCCGGCAGCCTCCATAGATNAA GTTATTGCANGAGTTCCTCTCCACGTCAAAGTACCAGCGTGGGAAGGATGCACGGCAAGGCCCAGTGACTGCGT TGGCGGTGCAGTATTCTTCATAGTTGAACATATCGCTGGAGTGGACTTCAGAATCCTGCCTTCTGGGAGCACTT GGGACAGAGGAATCCGCTGCATTCCTGCTGGTGGACCTCGGCCGCCACCACGCT

16446.2.edit

AGCGTGGTCGCGGCCGAGGTCCACCAGCAGGAATGCAGCGGATTCCTCTGTCCCAAGTGCTCCCAGAAGGCAGG ATTCTGAAGACCACTCCAGCGATATGTTCAACTATGAAGAATACTGCACCGCCAACGCAGTCACTGGGCCTTGC CGTGCATCCTTCCCACGCTGGTACTTTGACGTGGAGAGGAACTCCTGCAATAACTTCATCTATGGAGGCTGCCG GGGCAATAAGAACAGCTACCGCTCTGAGGAGGACCTGCCCGGGCCGCTCGA

16447.1.edit

58/101 16447.2.edit

16449.1.edit

16450.1.edit

16450.2.edit

59/101 16451.1.edit

16451.2.edit

TCGAGCGGCCGCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGNTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGTACCTCTGGTGAGGACCTCGGCCGCGACCACG
CT

16452.1.edit

16452.2.edit

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16453.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGCCGAACTGCCAGTGTACAGGGAAGATGTACATGTTATAGNTCTTCTCGAA GTCCCGGGCCAGCAGCTCCACGGGGTGGTCTCCTGCCTCCAGGCGCTTCTCATTCTCATGGATCTTCTTCACCC GCAGCTTCTGCTTCTCAGTCAGAAGGTTGTTGTCCTCATCCCTCTCATACAGGGTGACCAGGACGTTCTTGAGC CAGTCCCGCATGCGCAGGGGGAATTCGGTCAGCTCAGAGTCCAGGCAAGGGGGGATGTATTTGCAAGGCCCGAT GTAGTCCAAGTGGAGCTTGTGGCCCTTCTTGGTGCCCTCCAAGGTGCACTTTGTGGCAAAGAAGTGGCAGGAAG AGTCGAAGGTCTTGTTGTCATTGCTGCACACCTTCTCAAACTCGCCAATGGGGGCTGGGCAGACCTGCCCGGGC GGCCGCTCGA

16453.2.edit

16454.1.edit

AGCGTGGNTGCGGACGCCCACAAAGCCATTGTATGTATGTATTTANTTCAGCTGCAAANAATACCNCCAGCATCCACCTTACTAACCAGCATATGCAGACA

16454.2.edit

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AGCAGCCCAGCGAGGACTTGGTCTTAGTTGAGCAATTTGGCTAGGAGGATAGTATGCAGCACGGTTCTGAGTCT
GTGGGATAGCTGCCATGAAGNAACCTGAAGGAGGCGCTGGCTGGTANGGGTTGATTACAGGGCTGGGAACAGCT
CGTACACTTGCCATTCTCTGCATATACTGGNTAGTGAGGCGAGCCTGGCGCTCTTCTTTGCGCTGAGCTAAAGC
TACATACAATGGCTTTGNGGACCTCGGCCGCGACCACGCTT

61/101 16455.1.edit

TCGAGCGGCCGCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCAT TGTCATGACACCCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGC CTCTGCTGGTCTTCAAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCCACCA CGCT

16455.2.edit

16456.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGCTTNCTGCTCANGTGATTATCCTGAACCATCCAGGCCAAATAAGCGCCGGCTATGCCCCTGNATTGGATTGCCACACGGCTCACATTGCATGCAAGTTTGCTGAGCTGAAGGAAAAGATTGATC

16456.2.edit

62/101

16459.1.edit

16459.2.edit

16460.1.edit

TCGAGCGGCCCCGGGCAGGTCCATTTTCTCCCTGACGGNCCCACTTCTCCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCNTCCCCGAACCTTATGC
CTCTGCTGGGGCTTTCAGNGCCTCCACTATGATGNTGTAGGGGGGCACCTCTGGNGANGACCTCGGCCGCACCA
CGCT

16460.2.edit

Fig. 15BB

63/101

16461.1.edit

16461.2.edit

16463.1.edit

AGCGTGGNNGCGGCCGAGGTATAAATATCCAGNCCATATCCTCCCTCCACACGCTGANAGATGAAGCTGTNCAA AGATCTCAGGGTGGANAAAACCAT

16463.2.edit

64/101

16464.1.edit

16464.2.edit

AGCGTGGTTCGCGGCCGANGTCCTGTCAGAGTGGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTTC
TTCATCAGNGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGGCCCATGAGATGGTTG
TCTGAGAGAGAGGCTTCTTGNCCTGTCTTTTTCCTTCCAATCAGGGGCTCGCTCTTCTGATTATTCTTCAGGGCA
ATGACATAAATTGTATATTCGGGTCCCGGNTCCAGGCCAGTAATAGTANCCTCTGTGACACCCAGGCGGNGCCG
AGGGACCACTTCTCTGGGAGGAGACCCAGGCTTCTCATACTTGATGATGATGAACCGGTAATCCTGGCACGTGGCG
GCTGCCATGATACCAGCAAGGAATTGGGGTGTGGTGGCCAGGAAACGCAGGTTGGATGGNGCATCAATGGCAGT
GGAGGCCGTCGATGACCACAGGGGGAGCTCCGACATTGTCATTCAAGGTG

16465.1.edit

AGCGTGGNCGCGGCCGAGGTGCAGCGCGGGCTGTGCCACCTTCTGCTCTCTGCCCAACGATAAGGAGGGTNCCTGCCCCAGGAGAACATTAACTNTCCCCAGCTCGGCCTCTGCCGG

16465.2.edit

TCGAGCGGCCCCGGGCAGGTTTTTTTTTGCTGAAAGTGGNTACTTTATTGGNTGGAAAAGGGAGAAGCTGTGG
TCAGCCCAAGAGGGAATACAGAGNCCCGAAAAAGGGGAGGGCAGGTGGGCTGGAACCAGAACCAGACGCAGGCCAGGCA
GAAACTTTCTCTCCTCACTGCTCAGCCTGGTGGTGGCTGGAGCTCANAAATTGGGAGTGACACAGGACACCTTC
CCACAGCCATTGCGGCGGCATTTCATCTGGCCAGGACACTGGCTGTCCACCTGGCACTGGTCCCGACAGAAGCC
CGAGCTGGGGAAAGTTAATGTTCACCTGGGGGCAGGAACCCTCCTTATCATTGNGCAGAGAGCAGAAGGTGGCA
CAGCCCGCGCTGCACCTCGGCCGCGACCACGCT

16466.2.edit

TCGAGCGGCCCCGGGCAGGTCCACCATAAGTCCTGATACAACCACGGATGAGCTGTCAGGAGCAAGGTTGAT TTCTTTCATTGGTCCGGNCTTCTCCTTGGGGGNCACCCGCACTCGATATCCAGTGAGCTGAACATTGGGTGGCG TCCACTGGGCGCTCAGGCT

16467.2.edit

TCGAGCGGTTCGCCCGGGCAGGTCCACCACCCCAATTCCTTGCTGGTATCATGGCAGCCGCCCACGTGCCAGGA
TTACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGCGGTCCCTCGGCCCCGGCCCTGGT
GTCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGNCCTGAAGAATAA
TCANNAANAGCGANCCCCTGATTGGAAGGA

Fig. 15DD

PCT/US01/22635

65/101 01_16469.edit

02 16469.edit

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04_16470.edit

05_16471.edit

TCGAGCGGCCGCCGGGCAGGTCTCCCTTCTTGCGGCCCAGGGGCAGCGCATAGTGGGACTCGTACCACTGTCG
GTACGGTGTGCTGTCGATGAGCACGATGCAATTCTTCACCAGGGTCTTGGTACCGACCAGCTCGTTATTAGATG
CATTGTAGACAACATCGATGATCCTTGTTTTACGAGTACAACACTCTGAGCCCCAGGAGAAATTCCCCACGTCC
AACCTCAGGGCACGGTATTTCTTGTTACCTCCCCGCACACGGACTGTGTGGATGCGGCGGGGGCCAAGCTGACT
CCTGAGGAAGAAGAAGAATTTAAACAAAAAACGATCTAAAAAAATTCAGAAGAAAATATGATGAAAGGAAAAAAGAA
TGCCAAAATCAGCAGTCTCCTGGAGGAGCAGTTCCAGCAGGGCCAAGCTTCTTGCGTGCATCGCTTCAAGGCCGG
GACAGTGTGACCGAGCAGATGGCTATGTGCTAGAGGGCAAAGAAGTGGAGTTCTATCTTAAGAAAAATCAGGGCC
CAGAATGGTGNGTCTTCAACTAATCCAAAGGGGAGTTTCAGACCAGTGCAATCAGCAAAAAACATTGATACTGNT
GGCCAAATTTATTGGTGCAGGGCTTGCACANTANGANNGGCTGGGTCTTGGGGCTTGGAATTGGNACAAGCTTTG
GCAGCCTTTTCTTTGGTTTTGCCAAAAACCTTTTTGNTGAAGANGANACCTNGGGCGGACCCCTTAACCGATTCC
ACNCCNGGNGGCGTTCTANGGNCCCNCTTG

Fig. 15EE

66/101 06_16471.edit

AGCGTGGTCGCGGCCGAGGTCTGCTGCTTCAGCGAAGGGTTTCTGGCATAACCAATGATAAGGCTGCCAAAGAC
TGTTCCAATACCAGCACCAGAACCAGCCACTCCTACTGTTGCAGCACCTGCACCAATAAATTTGGCAGCAGTAT
CAATGTCTCTGCTGATTGCACTGGTCTGAAACTCCCTTTGGATTAGCTGAGACACCACCATTCTGGGCCCTGATT
TTCCTAAGATAGAACTCCAACTCTTTGCCCTCTAGCACATAGCCATCTGCTCGGTCACACTGTCCCGGCCTTGA
AGCGATGCACGCAAGAAGCTTGCCCTGCTGGAACTGCTCCTCCAGGAGACTGCTGATTTTTTCC
TTTCATCATATTTCTTCTGAATTTTTTTAGATCGTTTTTTTGTTTAAAATCTCTTCTTCCTCAGGAGTCAGCTTG
GCCCCCGCCGCATCCACACAGTCCGTGTGCGGGGAGGTAACAAGAAATACCGTGCCCTGAGGTTGGACGTGGGG
AATTTCTCCTGGGGCTCAGAGTGGTGTACTCGTAAAACAAGGATCATCGATGGTGNCTACAATGCATCTAATAA
CGAGCTGGGTCGGACCCAAAGAACCTGGNGAANAAATGGATCGNCTCATCGACAGGACACCGTACCCGACAGGG
GNACGANTCCCACTATGCGCTTGCCCCTGGGCCGCAANAAAAGGAAAACTGCCCGGGCGGCCNTCGAAAGCCCAA
TTNTGGAAAAAATCCATCACACTGGNGGCCNGTCGAGCATGCATNTANAGGGGCCCATTCCCCCTNANN

07 16472.edit

TCGAGCGGCCCCGGGCAGGTCCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAG ACTGGTGAGACCTGCGTGTACCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCAA GGACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCG ACCCTGCCGATGTGGACCTCGGCCGCGACCACGCT

08_16472.edit

AGCGTGGTCGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA GCCTTGGTTGGGGACCTGCCCGGGCGCCGCTCGA

09 16473.edit

TCGAGCGCCCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGCCTGAAGAATAAT CAGAAGAGCCAGCCCCTGATTGGAAGGAAAAAGAACAGACGAGCTTCCCCAACTGGTAACCCTTCCACACCCCAA TCTTCATGGACCAGAGATCTTGGATGTTCCTTCCACAGGTTCAAAAGACCCCTTTCGTCACCCCACCCTGGGTATG ACACTGGAAATGGTATTCAGGCTTCCTGGCACTTCTGGTCAGCAACCCAGTGTTGGGCAACAAATGATCTTTGAG GAACATGGNTTTAGGCGGACCACACCGCCCACAACGGCCCACACCCCCCATAAGGCATAGGCCAAGACCATACCCGCC GAATGTAGGACAAGAAGCCTNTNTNTCANACACCATNTNATGGGCCCCATTCCAGGACACTTCTGAGTACATCAT TTATGNCATCTGTGGCACTTGATGAAAACCCTTACAGTTCAGGGTTCTGGAACTTTTACCAGGCCTNTTACAGG ACTNGGCCGGACNCCTTAAGCCNATTNCACCCTGGGGCGTTCTANGGTCCCACTCGNNCACTGGNGAAAATGGC TACTGTN

67/101 11_16474.edit

12_16474.edit

13_16475.edit

TCGAGCGGCCGGCCGGGCAGGTCTGGTCCAGGATAGCCTGCGAGTCCTCCTACTGCTACTCCAGACTTGACATC
ATATGAATCATACTGGGGAGAATAGTTCTGAGGACCAGTAGGGCATGATTCACAGATTCCAGGGGGGCCAGGAG
AACCAGGGGACCCTGGTTGTCCTGGAATACCAGGGTCACCATTTCTCCCAGGAATACCAGGAGGGCCTGGATCT
CCCTTGGGGCCTTGAGGTCCTTGACCATTAGGAGGGCGAGTAGGAGCAGTTGGAGGCTGTGGGCAAACTGCACA
ACATTCTCCAAATGGAATTTCTGGGTTGGGGCAGTCTAATTCTTGATCCGTCACATATTATGTCATCGCAGAGA
ACGGATCCTGAGTCACAGACACATATTTGGCATGGTTCTGGCTTCCAGACATCTCTATCCGNCATAGGACTGAC
CAAGATGGGAACATCCTCCTTCAACAAGCTTNCTGTTGTGCCAAAAATAATAGTGGGATGAAGCAGACCGAGAA
GTANCCAGCTCCCCTTTTTGCACAAAGCNTCATCATGTCTAAAATATCAGACATGAGACTTCTTTGGGCAAAAAAA
GGAGAAAAAGAAAAAGCAGTTCAAAGTANCCNCCATCAAGTTGGTTCCTTGCCCNTTCAGCACCCGGGCCCCGT
TATAAAACACCCTNGGGCCGGACCCCCCTT

68/101 14_16475.edit

15 16476.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGTGC
GGGCGGGGTTCTTGCGGCTGCCCTCTGGGCTCCGGATGTTCTCGATCTGCTGGCTCAGGCTCTTGAGGGTGGTG
TCCACCTCGAGGTCACGGACCACACATTGGCATCATCAGCCCGGTAGTAGCGGCCACCATCGTGAGCCTT
CTCTTGANGTGGCTGGGGCAGGAACTGAAGTCGAAACCAGCGCTGGGAGACCAGGGGGACCAANAGGTCCAGG
AAGGGCCCGGGGGGACCAACAGGACCAGCATCACCAAGTGCGACCCGCGAGAACCTGCCCGGCCGNCCGCTCG
AA

16 16476.edit

69/101 17_16477.edit

18_16477.edit

AGCGTGGTTNGCGGCCGAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCACCAGGAAGCCCACGGGCTCCT GTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCTT CAATCCATNCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGTTCCAGGGAAACCACCGA GCACCCTGTGGTCCAACAACTCCTCTCTCACCAGGTCGTCCGGGTTTTCCAGGGTGACCATCTTCACCAGCCTT GCCAGGAGGACCAGCAGGACCAGCGTTACCAACCTGCCCGGGCGGCCGCTCGA

21_16479.edit

TCGAGCGCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCCCAATCTTGTAGTTCACACCAT TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCGACCACCGC

22 16479.edit

70/101 24_16480.edit

TCGAGCGNNCGCCCGGGCAGGTCCAGTAGTGCCTTCGGGACTGGGTTCACCCCCCAGGTCTGCGGCAGTTGTCAC
AGCGCCAGCCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCT
CCTACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTT
CCCAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTT
TACTTCCTCCTTCTCTACTGGAGCTTTCGTACCTTCCACTTCTGCTGTTGGTAAAATGGTGGATCTTCTATCAA
TTTCATTGACAGTACCCACTTCTCCCCAAACATCCAGGGAAAATAGTGATTTCAGTAGTGGAGAACCAAATT
ATGGGGCAGAAATAAGGGGCTTTTCCACAGGTTTTCCTTTTGGAGGAAGATTTCAGTGGTGACTTTAAAAGAATA
CTCAACAGTGTCTTCATCCCCATAGCAAAAGAAGAAACNGTAAATGATGGAAANGCTTCTGGAGGATGCCNNCATT
TAAGGGACNCCCAGAACTTCACCATCTACAGGACCTTCAGTTTACANNAAGNCACATANTCTGACTCANAA
AGGACCCCAAGTAGCNCCATGGNCAGCACTTTNAGCCTTTCCCCTGGGGAAAANNTTACNTTCTTAAANCCTNGG
CCNNGACCCCCTTAAGNCCAAATTNTGGAAAANTTCCNTNCNNCTGGGGGGCNGTTCNACATGCNTTTNAAGGG

25 16481.edit

26_16481.edit

27 16482.edit

TCGAGCGCCCCGGGCAGGTTGAATGGCTCCTCGCTGACCACCCCGGTGCTGGTGGTGGTACAGAGCTCCG ATGGGTGAAACCATTGACATAGAGACTGTCCCTGTCCAGGGTGTAGGGGCCCAGCTCAGTGATGCCGTGGGTCA GCTGGCTCAGCTTCCAGTACAGCCGCTCTCTGTCCAGTCCAGGGCTTTTGGGGTCAGGACGATGGGTGCAGACA GCATCCACTCTGGTGGCTGCCCCATCCTTCTCAGGCCTGAGCAAGGTCAGTCTGCAACCAGAGTACAGAGAGCT GACACTGGTGTTCTTGAACAAGGGCATAAGCAGACCCTGAAGGACACCTCGGCCGCGACCACGCT

Fig. 15JJ

71/101 28_16482.edit

29 16483.edit

31_16484.edit

37 16487.edit

72/101 38 16487.edit

CGAGCGGCCGCCGGGCAGGTTTGGAAGGGGGATGCGGGGGAAGAGAGACTGACGGTCCCCCCAGGAGTTCA GGTGCTGGGCACGGTGGGCATGTGTGAGTTTTGTCACAAGATTTGGGCTCAACTCTCTTGTCCACCTTGGTGTT GCTGGGCTTGTGATCTACGTTGCAGGTGTAGGTCTGGGTGCCGAAGTTGCTGGAGGGCACGGTCACCACGCTGC TGAGGGAGTAGAGTCCTGAGGACTGTAGGACAGACCTCGGCCGCGACCACGCT

39 16488.edit

NGGNNGGTCCGGNCNGNCAGGACCACTCNTCTTCGAAATA

41 16489.edit

AGCGTGGTCGCGGCCGAGGTCCTCACTTGCCTCCTGCAAAGCACCGATAGCTGCGCTCTGGAAGCGCAGATCTG
TTTTAAAGTCCTGAGCAATTTCTCGCACCAGACGCTGGAAGGGAAGTTTGCGAATCAGAAGTTCAGTGGACTTC
TGATAACGTCTAATTTCACGGAGCGCCACAGTACCAGGACCTGCCCGGGCGGCCGCTCGA

42 16489.edit

45 16491.edit

TCGAGCGGCCGCCCGGGCAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCTCGGCCGCGACCACGCT

Fig. 15LL

73/101 46_16491.edit

47_16492.edit

48_16492.edit

Fig. 15MM

74/101 49 16493.edit

55 16496.edit

56 16496.edit

TCGAGCGCCCCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCCCAATCTTGTAGTTCACACCAT
TGTCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA
AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA
GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCC
TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTCGGCCGCCACCACG
CT

59 16498.edit

75/101 60_16473.edit

60 16498.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCAATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAGTAACCACCACTCCCAAAAATGGACCAGGAC
CAACAAAAACTAAAACTGCAGGTCCAGATCAAACAGAAAATGACTATTGAAGGCTTGCAGCCCACAGTGGAGTAT
GTGGTTAGTGCTCAGAATCCAAGCGGAGAGAGACTCAGCCTCTGGTTCAGACTGCAGCACCAATGTTC
TGCACCAACTGACCTGAAGTTCACTCAGGTCACACCCACAAGCCTGAGCCGCCAGTGGACACCACCCAATGTTC
ACTCACTGGATATCGAGTGCGGGTGACCCCCCAAGGAGAAAGACCCGGCCGTGAAAAACCTTGCTCCT
GACAGCTCATCCGNGGGTGTATCAGGACTTATGGGGGACTTGCCCCGGCNGGCCGNTCGAAANCGAATTNTGAAA
TTTCCTTCNCACTGGGNGGCGNTTCGAGCTTNCTTNTANANGGCCCCAATTCNCCTNTAGNGGGTCGTN

61 16499.edit

AGCGTGGTCGCGGCCGAGGTCNAGGA

62 16483.edit

Fig. 1500

SUBSTITUTE SHEET (RULE 26)

76/101 63 16500.edit

AGCGTGGTCGCGGCCGAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCTCCAATCTTGTAGTTCACACCATTG
TCATGGCACCATCTAGATGAATCACATCTGAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTAAA
GCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGAGT
CATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGCCCACGGTAACAACCTCTTCCCGAACCTTATGCCTC
TGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAGGACCTGCCCGGGCGGCCCCGCT
CGA

64_16493.edit

64_16500.edit

PCT/US01/22635

77/101 16501.edit

WO 02/06317

16501.2.edit

GAGGACTGGCTCAGCTCCCAGTATAGCCGCTCTCTGTCCAGTCCAGGACCAGTGGGATCAAGGCGGAGGGTGCA GATGGCGTCCACTCCAGTGGCTGCCCCATGTTTCTCAAGTCTGAGCAAAGNCAGTCTGCAGCCAGAGTACAGAG GGCCAACACTGGTGCTCTTGAACAGGGACCTGAGCAGGCCCTGAAGGACCCTCTCCGTGGTGTTGAACTTCCTG GAGCCAGGGTGCTGCATGTTCTCCTCATACCGCAGGTTGTTGATGGTGAAGTTCAGTGTGAATGGCTCCTCGCT GACCACCC

16502.1.edit

16502.2.edit

TCGAGCGCCCCCGGCAGGTCCTGTCAGAGTGCACTGGTAGAAGTTCCAGGAACCCTGAACTGTAAGGGTT
CTTCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGTGTCCTGGAATGGGCCCATGAGATGGTT
GTCTGAGAGAGAGAGCTTCTTGTCCTACATTCGGCGGGTATGGTCTTGGCCTATGCCTTATGGGGGTGGCCGTTGT
GGGCGGTGTGGTCCGCCTAAAACCATGTTCCTCAAAGATCATTTGTTGCCCAACACTGGGTTGCTGACCAGAAG
TGCCAGGAAGCTGAATACCATTTCCAGTGTCATACCCAGGGNGGGTGACCAAAGGGGGTCNTTTNGACCTGGNG
AAAGGAACCATCCAAAANCTCTGNCCCATG

Fig. 15QQ

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16503.1.edit

16503.2.edit

AAGCGGCCGCCCGGGCAGGNNCAGNAGTGCCTTCGGGACTGGGNTCACCCCCAGGTCTGCGGCAGTTGTCACAG
CGCCAGCCCCGCTGGCCTCCAAAGCATGTGCAGGAGCAAATGGCACCGAGATATTCCTTCTGCCACTGTTCTCC
TACGTGGTATGTCTTCCCATCATCGTAACACGTTGCCTCATGAGGGTCACACTTGAATTCTCCTTTTCCGTTCC
CAAGACATGTGCAGCTCATTTGGCTGGCTCTATAGTTTGGGGGAAAGTTTGTTGAAACTGTGCCACTGACCTTTA
CTTCCTCCTTCTCTACTGGAGCTTTCCGTACCTTCCACTTCTGCTGNTGGNAAAAAGGGNGGAACNTCTTATCA
ATTTCATTGGACAGTANCCCNCTTTCTNCCCAAAACATNCAAGGGAAAATATTGATTNCNAGAGCGGATTAAGG
AACAACCCNAATTATGGGGGCCAGAAATAAAGGGGGGCTTTTCCACAGGTNTTTTCCT

16504.1.edit

TCGAGCGGCCCCGGGCAGGTCTGCAGGCTATTGTAAGTGTTCTGAGCACATATGAGATAACCTGGGCCAAGC
TATGATGTTCGATACGTTAGGTGTATTAAATGCACTTTTGACTGCCATCTCAGTGGATGACAGCCTTCTCACTG
ACAGCAGAGATCTTCCTCACTGTGCCAGTGGGCAGGAGAAAGAGCATGCTGCGACTGGACCTCGGCCGCCGACCA
CGCT

16504.2.edit

AGCGTGGTCGCGGCCGAGGTCCAGCATGCTCTTTCTCCTGCCCACTGGCACAGTGAGGAAGATCTCTG CTGTCAGTGAGAAGGCTGTCATCCACTGAGATGGCAGTCAAAAGTGCATTTAATACACCTAACGTATCGAACAT CATAGCTTGGCCCAGGTTATCTCATATGTGCTCAGAACACTTACAATAGCCTGCAGACCTGCCCGGGCGGCCGC TCGA

Fig. 15RR

79/101 16505.1.edit

CGAGCGGCCGCCCGGGCAGGTCCAGACTCCAATCCAGAGAACCACCAAGCCAGATGTCAGAAGCTACACCATCA
CAGGTTTACAACCAGGCACTGACTACAAGATCTACCTGTACACCTTGAATGACAATGCTCGGAGCTCCCCTGTG
GTCATCGACGCCTCCACTGCCATTGATGCACCCATCCAACCTGCGTTTCCTGGCCACCACCCCAATTCCTTGCT
GGTATCATGGCAGCCGCCACGTGCCAGGATTACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCA
GAGAAGTGGTCCCTCGGCCCCGCCCTGGTGNCACAGAAGCTACTATTACTGGCCTGGAACCGGGAACCGAATAT
ACAATTTATGTCATTGCCCTGAAGAATAATCANAAGAGCGAGCCCCTGATTGGAAGG

16505.2.edit

16506.1.edit

16506.2.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG
TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA
CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA
GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGTGC
GGGCGGGGTTCTTGCGGCTGCCCTCTGGGCTCCGGATGTTCTCGATCTGCTGGCTCAAGCTCTTGAAGGGTGGT
GTCCACCTCGAGGTCACGGACCTGCCCCGGAGCCGCCGCCGA

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16507.1.edit

AGCGTGGTCGCGGCCGAGGTCAAGAACCCCGCCCGCACCTGCCGTGACCTCAAGATGTGCCACTCTGACTGGAA
GAGTGGAGAGTACTGGATTGACCCCAACCAAGGCTGCAACCTGGATGCCATCAAAGTCTTCTGCAACATGGAGA
CTGGTGAGACCTGCGTGTACCCCCACTCAGCCCAGTGTGGCCCAGAAGAACTGGTACATCAGCAAGAACCCCCAAG
GACAAGAGGCATGTCTGGTTCGGCGAGAGCATGACCGATGGATTCCAGTTCGAGTATGGCGGCCAGGGCTCCGA
CCCTGCCGATGTGGACCTGCCCGNGCCGGNCCGCTCGAAAAGCCCNAATTTCCAGNCACACTTGGCCGGCCGTT
ACTACTG

16507.2.edit

TCGAGCGGCCGCCCGGGCAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCTCGGCCGCGACCACGCT

16508.1.edit

16508.2.edit

81/101 **16509.1**.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAACAACCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAAGTAACCACCACTCCCAAAAATGGACCAGGA
CCAACAAAAACTAAAACTGCAGGTCCAGATCAAACAGAAAATGGACTATTGAAGGCTTGCAGCCCACAGTAGAA
GTATGTGGNTAGGNGTCTATGCTCAGAATCCCAAGCCGGAGAAAGTCAGCCTTCTGGTTTAGACTGCAGTAACC
AACATTGATCGCCCTAAAGGACTGGNCATTCACTTGGATGGATGTCCAATTC

16509.2.edit

TCGAGCGGCCCCGGGCAGGTCCTTGCAGCTCTGCAGNGTCTTCTTCACCATCAGGTGCAGGGAATAGCTCAT
GGATTCCATCCTCAGGGCTCGAGTAGGTCACCCTGTACCTGGAAACTTGCCCCTGTGGGCTTTCCCAAGCAATT
TTGATGGAATCGACATCCACATCAGNGAATGCCAGTCCTTTAGGGCGATCAATGTTGGTTACTGCAGTCTGAAC
CAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGGGCTGCAAGCCTT
CAATAGTCATTTCTGTTTGATCTGGACCTGCAGTTTTAAGTTTTTGGTGGTCCTGNCCCATTTTTTGGGAAGTGG
GGGGTTACTCTGTAACCAGTAACAGGGGAACTTGAAGGCAGCCACTTGACACTAATGCTGTTGTCCTGAACATC
GGTCACTTGCATCTGGGGATGGTTTTGACAATTTCTGGTTCGGCAAATTAATGGAAATTGGCTTGCTGCTTGGC
GGGGCTGNCTCCACGGGCCAGTGACAGCATAC

16510.1.edit

16510.2.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGTAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGTTCCCCTGTTACTGGTTACAGAGTAACCACCACTCCCAAAAAATGGGACCAGGA
CCAACAAAAAACTAAAACTGCANGGTCCAGATCAAACAGAAATGACTATTGAAGGCTTGCAGCCCACAGTGGAG
TATGTGGGTTAGTGTCTATGCTCAGAATNCCAAGCGGAGAGAGTCAGCCTCTGGTTCAGACT

Fig. 15UU

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16511.1.edit

16511.2.edit

AGCGTGGTCGCGGCCGAGGTCTGTAGCTTCTGTGGGACTTCCACTGCTCAGGCGTCAGGCTCAGGTAGCTGCTG
GCCGCGTACTTGTTGTTGTTGCTTTGNTTGGAGGGTGTGGTGGTCTCCACTCCCGCCTTGACGGGGCTGCTATCTGC
CTTCCAGGCCACTGTCACGGCTCCCGGGTAGAAGTCACTTATGAGACACACCAGTGTGGCCTTGTTGGCTTGAA
GCTCCTCAGAGGAGGGTGGGAACAGAGTGACCGAGGGGGCAGCCTTGGGCTGACCTAGGACGGTCAGCTTGGTC
CCTCCGCCGAACACCCAATTGTTGTTGCCTGCATATGAGCTGCAGTAATAATCAGCCTCATCCTCAGCCTGGAG
CCCAGAGACNGTCAAGGGAGGCCCGTGTTTGCCAAGACTTGGAAGCCAGANAAGCGATCAGGGACCCCTGAGGG
CCGCTTTACNGACCTCAAAAAATCATGAATTTGGGGGGGCCTTTGCCTGGGNGTTGGTTAGTNACCAGNAAAACA
AAATTTCATAAAGCACCAACGTCACTGCTGGTTTCCAGTGCANGAANATGGTGAACTGAANTGTCC

16512.1.edit

16512.2.edit

TCGAGCGCCCCGGGCAGGTCCATACAGGGCTGTTGCCCAGGCCCTAGAGGNCATTCCTTGTACCCTGATCC
AGAACTGTGGGACCAGCACCATCCGTCTACTTACCTCCCTTCGGGCCAAGCACCCCAGGAGAACTGTGAGACC
TGGGGTGTAAATGGNGAGACGGGTACTTTGGTGGACATGAAGGAACTGGGCATATGGGAGCCATTGGCTGNGAA
GCTGCANACTTATAAGACAGCAGTGGAGACGGCAGTTCTGCTACTGCGAATTGATGACATCGTTTCAGGCCACA
AAAAGAAAGGCGATGACCANAGCCGGCAAGGCGGGGCTTCCTGATGCTGGACCTCGGCCGCCGACCACGCTT

Fig. 15VV

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16514.1.edit

AGCGTGGTCGCGGCCGAGGTCCACTAGAGGTCTGTGTGCCATTGCCCAGGCAGAGTCTCTGCGTTACAAACTCC
TAGGAGGGCTTGCTGTGCGGAGGGCCTGCTATGGTGTGCTGCGGTTCATCATGGAGAGTGGGGCCAAAGGCTGC
GAGGTTGTGGTGTCTGGGAAACTCCGAGGACAGAGGGCTAAATCCATGAAGTTTGTGGATGGCCTGATGATCCA
CAGCGGAGACCCTGTTAACTACTACGTTGACACTGCTGTGCGCCACGTGTTGCTCANACAGGGTGTGCTGGGCA
TCAAGGTGAAGATCATGCTGCCCTGGGACCCANCTGGCAAAAATGGCCCTTAAAAACCCCTTGCCNTGACCACG
TGAACCATTTGTGNGAACCCCCAAGATGAANATACTTGCCCCACCCCCCCATTC

16514.2.edit

16515.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGCCCTCCTGGCAAGGCTGGTGAAGATGGTCACCCTGGAAAACCCGGACGAC
CTGGTGAGAGAGAGTTGTTGGACCACAGGGTGCTCGTGGTTTCCCTGGAACTCCTGGACTTCCTGGCTTCAAA
GGCATTAGGGGACACAATGGTCTGGATGGATTGAAGGGACAGCCCGGTGCTCCTGGTGTGAAGGGTGAACCTGG
NGCCCCTGGTGAAAATGGAACTCCAGGTCAAACAGGAGCCCGNGGGCTTCCTGGNGAGAGAGAGGACGTGTTGGTG
CCCCTGGCCCANACCTGCCCGGGCGGCCGCTCNAAAAAGCCGAAATCCAGNACACTGGCGGCCGNTACTANTGGA
ATCCGAACTTCGGTACCAAAGCTTGGCCGTAATCATGGCCATAGCTTGTTCCCTGGGGNGGAAATTGGTATTCC
GCTNCCAATTCCACACAACATACCGAACCCGGAAAGCATTAAAGTGTAAAAGCCCTGGGGGGCCTAAATGANG
TGAGCNTAACTCNCATTTAATTGGCGTTGCGCTTCACTGCCCCCGCTTTTCCAGTCCGGGNA

16515.2.edit

TCGAGCGGCCGCCCGGGCAGGTCTGGGCCAGGGGCACCAACACGTCCTCTCTCACCAGGAAGCCCACGGGCTCC
TGTTTGACCTGGAGTTCCATTTTCACCAGGGGCACCAGGTTCACCCTTCACACCAGGAGCACCGGGCTGTCCCT
TCAATCCATCCAGACCATTGTGNCCCCTAATGCCTTTGAAGCCAGGAAGTCCAGGAGGTTCCAGGGAAACCACGA
GCACCCTGTGGTCCAACAACTCCTCTCTCACCAGGTCGTCCGGGTTTTCCAGGGTGACCATCTTCACCAGCCTT
GCCAGGAGGGCCAGACCTCGGCCGCCGACCACGCT

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16516.1.edit

ANCGTGGTCGCGGCCGAGGTCCTCACCAGAGGTGNCACCTACAACATCATAGTGGAGGCACTGAAAGACCANCA GAGGCATAAGGTTCGGGAAGAGG

16516.2.edit

TCGAGCGGCCGCCGGGCAGGTCCATTTTCTCCCTGACGGTCCCACTTCTCCCAATCTTGTAGTTCACACCAT TGTCATGGCACCACGCGCACACTTTTCCCAAATGACCACTTCCAAAGCCTAAGCACTGGCACAACAGTTTA AAGCCTGATTCAGACATTCGTTCCCACTCATCTCCAACGGCATAATGGGAAACTGTGTAGGGGTCAAAGCACGA GTCATCCGTAGGTTGGTTCAAGCCTTCGTTGACAGAGTTGTCCACGGTAACAACCTCTTCCCGAACCTTATGCC TCTGCTGGTCTTTCAGTGCCTCCACTATGATGTTGTAGGTGGCACCTCTGGTGAAGGACCTCNGNCCNGAACAAC GCTTAAGCCCGNATTCTGCAGAATAATCCCATCACACTTGGCGGCCGCCTTCGANCATGCATCNTAAAAGGGGGCC CCAATTTCCCCCTTATAAGNGAANCCGTATTTNCCAATTTCACTGGNCCCGCCGNTTTTACAAACGNCGGTGAA CTGGGGGAAAAACCCTGGCGGTTACCCAACTTTAATCGCCNTTGGCAGCACAATCCCCCCTTTTCGNCCANCNTG GGCGTAAATAACCGAAAA

16517.1.edit

16518.1.edit

AGCGTGGTCGCGGCCGAGGTCTGAGGTTACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGT
TCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACG
TACCGGGNGGTCAGCGTCCTCACCGTCCTGCACCAGAATTGGTTGAATGGCAAGGAGTACAAGNGCAAGGTTTC
CAACAAAGCCNTCCCAGCCCCCNTCGAAAAAACCATTTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGT
ACACCCTGCCCCCATCCCGGGAGGAAAAAGANCAANAACCNGGTTCAGCCTTAACTTGCTTGGTCNAANGCTTTT
TATCCCAACGNACTTCCCCCNTGGAANTGGGAAAAACCAATGGGCCAANCCGAAAAACAATTACAANAACCCC

16518.2.edit

Fig. 15XX

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16519.1.edit

AGCGTGGTCGCGGACGANGTCCTGTCAGAGTGGNACTGGTAGAAGTTCCANGAACCCTGAACTGTAAGGGTTCT TCATCAGTGCCAACAGGATGACATGAAATGATGTACTCAGAAGNGNCCTGGAATGGGGCCCATGANATGGTTGC C

16519.2.edit

TCGAGCGCCCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGGAACCGAATATACAATTTATGTCATTGCCCTGAAGAATAAT CAGAAGAGCGAGCCCCTGATTGGAAGGAAAAAGACCAGACGAGCTTCCCCAACTGGTAACCCTTCCACACCCCAA TCTTCATGGACCAGAGATCTTGGATGTTCCTTCCACAGTTCAAAAGACCCCTTTCGGCACCCCCCTGGGTATG AACCTGGGAAAANGGNANTTAANCTTTCCTGGCA

16520.1.edit

AGCGTGGTCGCGGCCGAGGTCTGGGATGCTCCTGCTGTCACAGTGAGATATTACAGGATCACTTACGGAGAAAC
AGGAGGAAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGGAGCAAGTCTACAGCTACCATCAGCGGCCTTAAAC
CTGGAGTTGATTATACCATCACTGTGTATGCTGTCACTGGCCGTGGAGACAGCCCCGCAAGCAGCAGCAAGCCAATT
TCCATTAATTACCGAACAGAAATTGACAAACCATCCCAGATGCAAGTGACCGATGTTCAGGACAACAACAGCATTAG
TGTCAAGTGGCTGCCTTCAAGGTNCCCTGGTACTGGGTTACAGANTAACCACCACTCCCAAAAATGGACCAGGA
ACCACAAAAACTTAAACTGCAGGGTCCAGATCAAAACAGAAATGACTATTGAANGCTTGCAGCCCACAGTGGGA
GTATGNGGGTAGTGNCTATGCTTCAGAATCCAAGCGGAAAAANGTCAAGCCTTNTGGGTTCAA

16520.2.edit

TCGAGCGGCCGCCCGGGCAGGTCCTTGCAGCTCTGCAGTGTCTTCTTCACCATCAGGTGCAGGGAATAGCTCAT GGATTCCATCCTCAGGGCTCGAGTAGGTCACCCTGTACCTGGAAACTTGCCCCTGTGGGCTTTCCCAAGCAATT TTGATGGAATCGACATCCACATCAGTGAATGCCAGTCCTTTAGGGCGATCAATGTTGGTTACTGCAGNCTGAAC CAGAGGCTGACTCTCTCCGCTTGGATTCTGAGCATAGACACTAACCACATACTCCACTGTGGGCTGCAANCCTT CAATAANNCATTTCTGTTTGATCTGGACC

16521.2.edit

TCGAGCGCCCCCGGGCAGGTCTGGTGGGGTCCTGGCACACGCACATGGGGGNGTTGNTCTNATCCAGCTGCC CAGCCCCCATTGGCGAGTTTGAGAAGGTGTGCAGCAATGACAACAANACCTTCGACTCTTCCTGCCACTTCTTT GCCACAAAGTGCACCCTGGAGGGCCACCAAGAAGGGCCACAAGCTCCACCTGGACTACATCGGGCCTTGCAAATA CATCCCCCCTTGCCTGGACTCTGAGCTGACCGAATTCCCCCCTTGCGCATGCGGACTGGCTCAAGAACCGTCCT GGCACCCTTGTATGANAGGGATGAAGACACNACCC

Fig. 15YY

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16522.1.edit

AGCGTGGTCGCGGCCGAGGTCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCT CCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCCAAGGTGGACAAGAGA GTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGACCGTC AGTCTTCCTCTTCCCCCGCATCCCCCTTCCAAACCTGCCCGGGCGGCCGCTCGAAAGCCGAATTCCAGCACACT GGCGGCCGGTACTAGTGGANCCNAACTTGGNANCCAACCTGGNGGAANTAATGGGCATAANCTGTTTCTGGGGG GAAATTGGTATCCNGTTTACAATTCCCNCACAACATACGAGCCGGAAGCATAAAAGNGTAAAAGCCTGGGGGNG GCCTANTGAAGTGAAGCTAAACTCACATTAATTNGCGTTGCCGCTCACTGGCCCGCTTTTCCAGC

16522.2.edit

TCGAGCGCCCCCGGGCAGGTTTGGAAGGGGGATGCGGGGGAAGAGAGACTGACGGTCCCCCAGGAGTTC AGGTGCTGGGCACGGTGGGCATGTGTGAGTTTTGTCACAAGATTTGGGCTCAACTCTCTTGTCCACCTTGGTGT TGCTGGGCTTGTGATCTACGTTGCAGGTGTAGGTCTGGGNGCCGAAGTTGCTGGAGGGCACGGTCACCACGCTG CTGAGGGAGTAGAGTCCTGAGGACTGTANGACAGACCTCGGCCGNGACCACGCTAAGCCGAATTCTGCAGATAT CCATCACACTGGCGGCCGCCCTCCGAGCCATGCATTTTAGAGG

16523.1.edit

AGCGTGGNCGCGGACGANGACAACAACCCC

16523.2.edit

TCGAGCGGCCGCCCGGGCAGGNCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATC
GGTCATGCTCTTGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGNACCAGTTCTTCTGGGCCA
CACTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTG
CAGCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAGTGGCACATCTTGAGGTCACGGCAGGT
GCGGGCGGGGTTCTTGACCT

16524.1.edit

AGCGTGGTCGCGGCCGAGGTCCAGCCTGGAGATAANGGTGAAGGTGGTGCCCCCGGACTTCCAGGTATAGCTGG ACCTCGTGGTAGCCCTGGTGAGAGAGGTGAAACTGGCCCTCCAGGACCTGCTGGTTTCCCTGGTGCTCCTGGAC AGAATGGTGAACCTGGNGGTAAAGGAGAAAGAGGGGCTCCGGNTGANAAAGGTGAAGGAGGCCCTCCTGNATTG GCAGGGGCCCCANGACTTAGAGGTGGAGCTGGCCCCCCTGGCCCCGAAGGAGGAAAGGGTGCTGCTGGTCCTCC TGGGCCACCTGG

PCT/US01/22635

WO 02/06317

87/101 16524.2.edit

TCGAGCGGCCGCCCGGGCAGGTCTGGGCCAGGAGGACCAATAGGACCAGTAGGACCCCTTGGGCCATCTTTCCC
TGGGACACCATCAGCACCTGGACCGCCTGGTTCACCCTTGTCACCCTTTGGACCAGGACTTCCAAGACCTCCTC
TTTCTCCAGGCATTCCTTGCAGACCAGGAGTACCANCAGCACCAGGTGGCCCAGGAGGACCAGCAGCACCCTTT
CCTCCTTCGGGACCAGGGGGCCCAGCTCCACCTCTAAGTCCTGGGGCCCCTGCCAATCCAGGAGGCCCTCCTTC
ACCTTTCTCACCCGGAGCCCCTCTTTCT

16526.1.edit

16526.2.edit

ATGCGNGGTCGCGGCCGANGACCANCTCTGGCTCATACTTGACTCTAAAGNCNTCACCAGNANTTACGGNCATT GCCAATCTGCAGAACGATGCGGGCATTGTCCGCANTATTTGCGAAGATCTGAGCCCTCAGGNCCTCGATGATCT TGAAGTAANGGCTCCAGTCTCTGACCTGGGGTCCCTTCTTCTCCCAAGTGCTCCCGGATTTTGCTCTCCAGCCTC CGGTTCTCGGTCTCCAAGNCTTCTCACTCTGTCCAGGAAAAGAGGCCAGGCGGNCGATCAGGGCTTTTGCATGG ACT

16527.1.edit

16527.2.edit

TCGAGCCGCCCGGGCAGGTCTGCCAACACCAAGATTGGCCCCCGCCGCCGCCATCCACACAGTTNGTGTGCGGGGAGGTAACAAGAAATACCGTGCCCTGAGGNTGGACGNGGGGAATTTCTCCTGGGGCTCAGAGTGTTGTACTCGTAAAACAAGGATCATCGATGTTGTCTACAATGCATCTAATAACGAGCTGGTTCGTACCAAGACCCTGGTGAAGAATTGCATCGTGCTCATNGACAGCACCACCGTACCGACAGTGGGTACCGAAGTCCCACTATGCNCCT

Fig. 15AAA

SUBSTITUTE SHEET (RULE 26)

88/101 16528.1.edit

TCGAGCGGCCGCCCGGGCAGGTCCACCACACCCAATTCCTTGCTGGTATCATGGCAGCCGCCACGTGCCAGGAT TACCGGCTACATCATCAAGTATGAGAAGCCTGGGTCTCCTCCCAGAGAAGTGGTCCCTCGGCCCCGCCCTGGTG TCACAGAGGCTACTATTACTGGCCTGGAACCGGAACCGAATATACAATTTATGTCATTGCCCTGAAG

16528.2.edit

AGCGTGNTCNCGGCCGAGGATGGGGAAGCTCGNCTGTCTTTTTCCTTCCAATCAGGGGCTNNNTCTTCTGATTA
TTCTTCAGGGCAANGACATAAATTGTATATTCGGNTCCCGGTTCCAGNCCAGTAATAGTAGCCTCTGTGACACC
AGGGCGGGCCGAGGGACCACTTCTCTGGGAGGAGACCCCAGGCTTCTCATACTTGATGATGAAGCCGGTAATCC
TGGCACGTGGGCGGCCGCTGCCATGATACCACCCAANGAATTGGGTGTGGTGGACCTGCCCGGGCGGCCGCTCGAAA
ANCCGAATTCNTGCAAGAATATCCATCACACTTGGGCGGGCCGNTCGAACCATGCATCNTAAAAGGGCCCCAAT
TTCCCCCCTATTAGGNGAAGCCNCATTTAACAAATTCCACTTGG

16529.1.edit

TCGAGCGCCCCCGGGCAGGTCTCGCGGTCGCACTGGTGATGCTGGTCCTGTTGGTCCCCCCGGCCCTCCTGG ACCTCCTGGTCCCCCTGGTCCTCCCAGCGCTGGTTTCGACTTCAGCTTCCTGCCCCAGCCACCTCAAGAGAAGG CTCACGATGGTGGCCGCTACTACCGGGCTGATGATGCCAATGTGGTTCGTGACCGTGACCTCGAGGTGGACACC ACCCTCAAGAGCCTTGAGCCAGCAGAATCGAAAACATTCGGAACCCAAGAAGGGCAAGCCCGCAAAGAAACCCC GCCCGCACCTGGCCGNGAACCTCCAAGAANGTGCCCACNTCTTGACTGGGAAAAAAAAGGGAAAAANTACTTGGAA TTGGAC

16529.2.edit

AGCGTGGTCGCGGCCGAGGTCCACATCGGCAGGGTCGGAGCCCTGGCCGCCATACTCGAACTGGAATCCATCGG TCATGCTCTCGCCGAACCAGACATGCCTCTTGTCCTTGGGGTTCTTGCTGATGTACCAGTTCTTCTGGGCCACA CTGGGCTGAGTGGGGTACACGCAGGTCTCACCAGTCTCCATGTTGCAGAAGACTTTGATGGCATCCAGGTTGCA GCCTTGGTTGGGGTCAATCCAGTACTCTCCACTCTTCCAGTCAGAAGTGGCACATCTTGAGGTCACGGCAGGGT GCGGGCGGGGTTCTTGCGGGCTGCCCTTCTGGGCTCCCGGAATGTTCTNNGAACTTGCTGG

89/101 16530.1.edit

16530.2.edit

16531.1.edit

TCGAGCGGCCGCCCGGGCAGGTGTTTCAGAGGTTCCAAGGTCCACTGTGGAGGTCCCAGGAGTGCTGGTGGTGG GCACAGAGGTCCGATGGGTGAAACCATTGACATAGAGACTGTTCCTGTCCAGGGTGTAGGGGCCCAGCTCTTTG ATGCCATTGGCCAGTTGGCTCAGCTCCCAGTACAGCCGCTCTCTGTTGAGTCCAGGGGCTTTTGGGGTCAAGATG ATGGATGCAGATGGCATCCACTCCAGTGGCTGCTCCATCCTTCTCGGACCTGAGAGAGGTCAGTCTGCAGCCAG AGTACAGAGGGCCAACACTGGTGTTCTTTGAATA

16531.2.edit

16532.1.edit

90/101 01 16558.3.edit

AGCGTGGTCGCCGAGGTGAGCCACAGGTGACCGGGGCTGAAGCTGGGGCTGCTGGNCCTGCTGGTCCTG

02 16558.4.edit

CAGCNGCTCCNACGGGGCCTGNGGGACCAACAACACCGTTTTCACCCTTAGGCCCTTTGGCTCCTCTTTCTCCT
TTAGCACCAGGTTGACCAGCAGCNCCANCAGGACCAGCAAATCCATTGGGGCCAGCAGGACCGACCTCACCACG
TTCACCAGGGCTTCCCCGAGGACCAGCAGGACCAGCAGCACCAGCTTCGCCCCGGTCACCTGTGG
CTCACCTCGGCCGCGACCACGCT

03 16535.1.edit

TCGAGCGGTCGCCCGGGCAGGTCCACCGGGATAGCCGGGGGTCTGGCAGGAATGGGAGGCATCCAGAACGAGAA GGAGACCATGCAAAGCCTGAACGACCGCCTGGCCTCTTACCTGGACAGAGTGAGGAGCCTGGAGACCGANAACC GGAGGCTGGANAGCAAAATCCGGGAGCACTTGGAGAAGAAGAAGGGACCCCAGGTCAAGAGACTGGAGCCATTACTT CAAGATCATCGAGGGACCTGGAGG

04_16535.2.edit

AGCGNGGTCGCGGCCGAGGTCCAGCTCTGTCTCATACTTGACTCTAAAGTCATCAGCAGCAAGACGGGCATTGT CAATCTGCAGAACGATGCGGGCATTGTCCGCAGTATTTGCGAAGATCTGAGCCCTCAGGTCCTCGATGATCTTG AAGTAATGGCTCCAGTCTCTGACCTGGGGTCCCTTCTTCTCCAAGTGCTCCCGGATTTTGCTCTCCAGCCTCCG GTTCTCGGTCTCCAGGCTCCTCACTCTGTCCAGGTAAGAAGGCCCAGGCGGTCGTTCAGGCTTTGCATGGTCTC CTTCTCGTTCTGGATGCCTCCCATTCCTGCCAGACCC

05 16536.1.edit

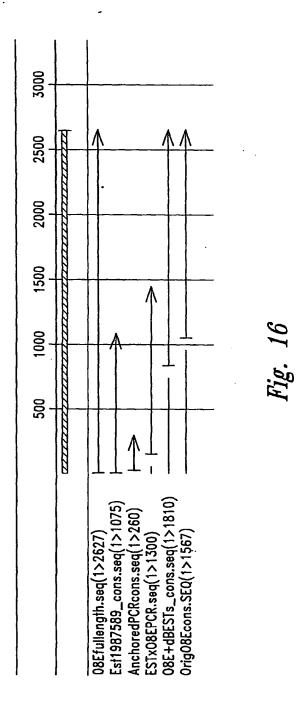
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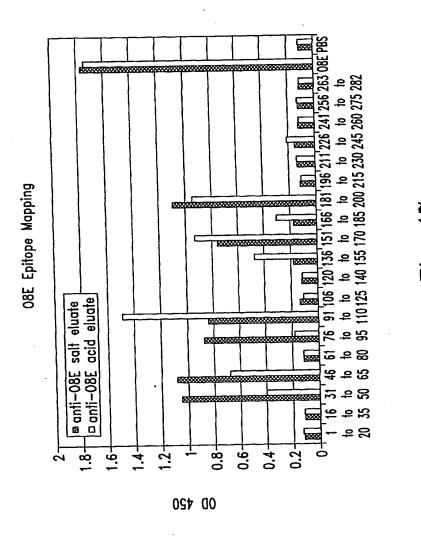
Fig. 15DDD

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08_16537.2.edit

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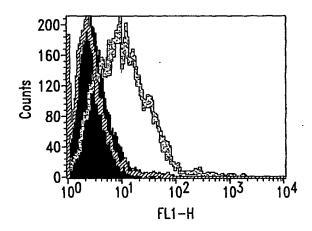




SUBSTITUTE SHEET (RULE 26)

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OBE Surface Expression

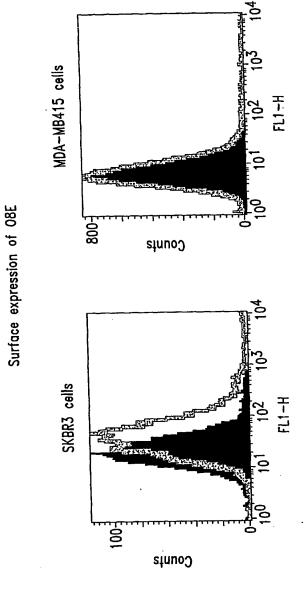


B305D/HEK stained with anti-08E antibody

08E/HEK stained with anti-08E antibody

08E/HEK stained with an irrelevant antibody

Fig. 18

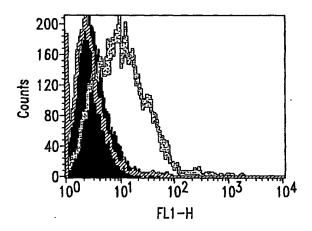


Black; irrelevant antibody Light gray; anti-08E antibody

Fig. 19

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08E Surface Expression

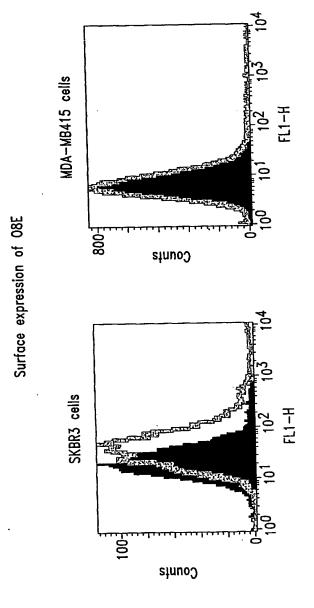


B305D/HEK stained with anti-08E antibody

O8E/HEK stained with anti-08E antibody

O8E/HEK stained with an irrelevant antibody

Fig. 20



Black; Irrelevant antibody Light Grey; Anti-08E antibody

Fig 21

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08E expression in HEK293 Cells (probed with anti-08E rabbit polyclonal sera #2333L)

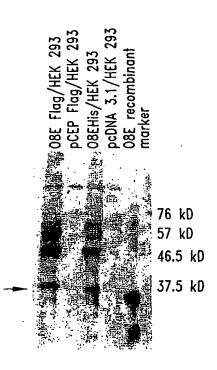


Fig. 22

							9	99	/	1() 1	ļ									
	1:2048000	100	 	0.07	0.07	15	2 :	0.16	0 16	2	0.07		200	200		0.14	D 14	3	0.14		
	1024000) (0.0	9.00	90:0	760	17.4	57.	26.0	3.0	20		0.07	20.0	000	0.20	200	0.20	0.20		
	1.512000	1,01200	0.07	0.07	0.07	0,0	0 . 40	0.40	5	0.40	700	200	0:0	200	70'0	0.32	0.75	6.33	0.33		
	255000		0.0	90:0	200		 20.0	99.0	200	0.0	70.0	70.0	0:0	70.0	0.0/	0.58	60	0.30	0.58		
Jilutior	4.40000	21:1	90.0	0.00	٤	3	<u>=</u>	100		3	5))	0.0	66.4	3	0.92		0.58	8		
Antibody Dilutions	0007	3	0.07	0.07	0.07	3	<u>.</u>	1.57		<u> </u>	5) ⊃	0.07		0.07	141		*	1 43	2	
Ant	1	37000 1:37000		200	100	200	7.08 7.08	3,0	3	, 8	15.0	≥	0.07		0:0	1.	1	<u>56</u>	~ %	3	
	0000	1:1000 1:2000 1:4000 1:8000 1:15000	20.0	0.07	200	3	7.28	3 48	2	2.53		0:0	9	3	89.0	0.50	3	2.37	226	3	
			5	200	2 6	0.0	2.70	60	3	2,69		9.0	70.0	3	9.0	3 48	?	29.	9.54	4	l
		\$ 5	ã	3 5	3 3	0.0	274	-	177	274		90.0	900	3	90.0	264	1017	251	100	/07	
		1.200 1.200 1.200	g	3 2	3	<u> </u>	2	1	11.7	976	1	0.07	2	3	0.07	7, 6	?	2.76	5	9/7	
		5000	E	3 5	3	===	293	100	3.7	9 07	_	0.09		9	0.08	17.6	2.7	2.73		7.7	
	Sera Sample		00/01/11/11/10/00	Preimmune sera (#23/0L):11/10/39		Average	. AGE (#2576K).1 /11 /2000	Q-00E (#73) 01/11/ 11/ 700		A A	Average	B / 11 / 11 / 10 / 99			Average	000/11/1/2550/	a -08F (#2332L):1/11/2000			Average	
	Antigen	7	_		(#632-24)																_

affi-pure 08E #2576L 739.87A&B

		739.878 1.7mg/ml 3mg
Date: 5/2/2000	08E polyclonal 2576L, 1/11/2000 affinity PBS #705, p150	739.87A 1.4mg/ml 18mg
	Antibody Name Rabbit #, Bleed Date Purification Method Buffer Notebook	lot # Antibody Concentration Initial Amount

Sera Sample 1:1000 preimmune sera (2576L) 0.15 α-08Ε (2576Κ):2/8/2000 2.74 Ανεταge 0.14 Ανεταge 2.73 αffinity pure α-08Ε poly 2.69 salt peak 739-87A 2.59 Ανεταge 2.54 αffinity pure α-08Ε poly 2.69 αcid peak 739-67Β 2.64	1:1000 1:2000 0.15 0.11 0.14 0.10 0.14 0.10 2.74 2.71 2.72 2.68 2.73 2.70 2.69 2.60 2.59 2.60 2.59 2.60 2.59 2.48 2.48 2.54 2.46 2.39 2.65 2.65	1:1000 1:2000 1:4000 0.15 0.11 0.09 0.14 0.10 0.09 0.14 2.71 2.63 2.72 2.68 2.64 2.73 2.70 2.63 2.69 2.60 2.50 2.59 2.48 2.38 2.46 2.39 2.40 2.65 2.65 2.61	1:1000 1:2000 1:4000 1 0.15 0.11 0.09 0.14 0.10 0.09 0.14 0.10 0.09 2.72 2.68 2.64 2.73 2.70 2.63 2.69 2.60 2.50 2.59 2.48 2.38 2.64 2.54 2.44 2.46 2.39 2.40 2.65 2.65 2.61	1:1000 1:2000 1:4000 1:8000 1: 0.15	1:1000 1:2000 1:4000 1:8000 1:16000 1:000 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.14 0.10 0.14 0.14 0.18 0.18 0.19 0.19 0.19 0.19 0.19 0.19 0.19 0.19	1:1000 1:2000 1:4000 1:8000 1:16000 1:32000 0.15 0.11 0.09 0.08 0.08 0.07 0.14 0.10 0.09 0.08 0.07 0.07 2.74 2.71 2.63 2.49 2.29 1.87 2.72 2.68 2.64 2.47 2.26 1.93 2.73 2.70 2.63 2.48 2.27 1.30 2.59 2.60 2.50 2.21 1.83 1.34 2.59 2.48 2.38 2.21 1.83 1.34 2.46 2.39 2.40 2.34 2.08 1.73 2.46 2.39 2.40 2.34 2.08 1.73 2.65 2.65 2.61 2.45 2.14 1.76	1:1000 1:2000 1:4000 1:8000 1:16000 1:32000	Antibody Dilutions 1:1000 1:2000 1:4000 1:16000 1:52000 1:64000 1:128000 1:1000 1:2000 1:4000 1:10000 1:52000 1:64000 1:128000 1:1000 0.14 0.10 0.09 0.08 0.07 0.07 0.07 0.07 0.07 0.07 0.07	Antibody Dilutions 1:1000 1:2000 1:4000 1:16000 1:15000 1:52000 1:75000 1:15000 1:25000 1:75000 1:15000 1:25000 1:75000 1:25000 1:75000 1:25000 1:75000 1:25000 1:75000 1:25000 1:75000 1:25000 1:75000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 1:25000 0:08 0:07 0:07 0:07 0:07 0:07 0:07 0		Antigen	on Plate	08E prei	#632-24		a –0.			affi	<i>V</i>		affi		
1:1000 0.15 0.14 2.72 2.73 2.73 2.69 2.59 2.59 2.59 2.54 2.46 2.46 2.46	2.70 2.71 2.71 2.70 2.70 2.70 2.68 2.60 2.60 2.54 2.39 2.39 2.54	0.11 0.09 0.10 0.09 0.10 0.09 0.10 0.09 0.10 0.09 2.71 2.63 2.68 2.64 2.70 2.53 2.60 2.50 2.48 2.38 2.54 2.44 2.39 2.40 2.66 2.50	1:2000 1:4000 0.11 0.09 0.10 0.09 0.10 0.09 2.71 2.63 2.68 2.64 2.70 2.63 2.60 2.50 2.48 2.38 2.34 2.44 2.39 2.40 2.66 2.61	1.2000 1.4000 1.8000 0.11 0.09 0.08 0.10 0.09 0.08 0.10 0.09 0.08 2.71 2.63 2.49 2.68 2.64 2.47 2.70 2.63 2.48 2.60 2.50 2.21 2.48 2.38 2.21 2.54 2.44 2.21 2.54 2.44 2.21 2.55 2.40 2.34 2.66 2.61 2.45	1.2000 1:4000 1:8000 1:16000 0.11 0.09 0.08 0.08 0.10 0.09 0.08 0.07 0.10 0.09 0.08 0.07 2.71 2.63 2.49 2.29 2.68 2.64 2.47 2.26 2.70 2.63 2.48 2.27 2.60 2.50 2.21 1.83 2.48 2.38 2.21 1.83 2.54 2.44 2.21 1.83 2.59 2.40 2.34 2.08 2.56 2.61 2.45 2.14	1.2000 1.4000 1.8000 1.16000 1.32000 0.11 0.09 0.08 0.08 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.10 0.09 0.08 0.07 0.00 0.00 0.00 0.00 0.00 0.00	1.2000 1.4000 1.8000 1.16000 1.32000 0.11 0.09 0.08 0.08 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.10 0.10 0.10 0.10 0.10 0.10	Antibody Dilutions 1:2000 1:4000 1:8000 1:16000 1:12000 1:4000 1:8000 1:16000 1:32000 1:64000 1:12000 0.11 0.09 0.08 0.08 0.07 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.07 0.07 0.07 0.07	Antibody Dilutions 1:2000 1:4000 1:8000 1:16000 1:32000 1:64000 1:128000 1:256000 0.11 0.09 0.08 0.07 0.07 0.07 0.07 0.10 0.09 0.08 0.07 0.07 0.07 0.07 2.71 2.63 2.49 2.29 1.87 1.39 0.92 0.57 2.68 2.64 2.47 2.26 1.93 1.42 0.94 0.57 2.70 2.63 2.48 2.27 1.90 1.41 0.93 0.57 2.60 2.50 2.21 1.83 1.34 0.99 0.64 0.38 2.48 2.38 2.21 1.82 1.33 1.00 0.63 0.37 2.39 2.40 2.34 2.08 1.73 1.29 0.81 0.49 2.50 2.61 2.45 2.14 1.76 1.30 0.82 0.48	Silo:	Sera Sample		mmune sera (2576L)	•	Average	3E (2576K):2/8/2000		Average			Average			
	1;2000 0.11 0.10 0.10 2.71 2.68 2.70 2.60 2.54 2.54 2.54 2.54 2.54	2.44 2.44 2.44 2.46 2.46 2.44 2.46 2.46	1;4000 0.09 0.09 0.09 2.64 2.25 2.25 2.24 2.44 2.40 2.40	1:4000 1:8000 0.09 0.08 0.09 0.08 0.09 0.08 2.63 2.49 2.64 2.47 2.50 2.21 2.40 2.21 2.40 2.34 2.40 2.34 2.61 2.45	1:4000 1:8000 1:16000 0.09 0.08 0.07 0.09 0.08 0.07 0.09 0.08 0.07 2.63 2.49 2.29 2.64 2.47 2.26 2.50 2.21 1.83 2.38 2.21 1.83 2.44 2.21 1.83 2.40 2.34 2.08 2.40 2.34 2.08	1:4000 1:8000 1:16000 1:32000	1:4000 1:8000 1:16000 1:32000	Antibody Dilutions 1:4000 1:3000 1:64000 1:128000 0.09 0.08 0.07 0.07 0.07 0.07 0.09 0.09 0.08 0.07 0.07 0.07 0.09 0.09 0.08 0.07 0.07 0.07 0.09 0.09 0.08 0.07 0.07 0.07 0.09 0.09 0.09 0.09 0.29 1.87 1.39 0.92 0.50 0.21 1.83 1.34 0.99 0.64 0.38 0.21 1.82 1.34 0.99 0.64 0.34 0.21 1.83 1.34 0.99 0.64 0.53 0.24 0.24 0.21 1.83 1.34 0.99 0.65 0.24 0.24 0.24 0.25 0.24 0.08 0.05 0.24 0.24 0.25 0.24 0.08 0.05 0.06 0.34 0.25 0.24 0.08 0.05 0.08 0.06 0.34 0.08 0.05 0.08 0.06 0.34 0.08 0.08 0.08 0.09 0.08 0.09 0.09 0.09	Antibody Dilutions 1:4000 1:8000 1:16000 1:32000 1:128000 1:256000 0.09 0.08 0.07 0.07 0.07 0.07 0.07 0.09 0.08 0.07 0.07 0.07 0.07 0.07 2.63 2.49 2.29 1.87 1.39 0.92 0.57 2.64 2.47 2.26 1.93 1.42 0.94 0.57 2.50 2.21 1.83 1.34 0.99 0.64 0.57 2.50 2.21 1.83 1.34 0.99 0.64 0.38 2.44 2.21 1.83 1.34 0.99 0.64 0.37 2.40 2.34 2.08 1.73 1.00 0.65 0.37 2.40 2.34 2.08 1.75 1.29 0.81 0.49 2.41 1.76 1.30 0.82 0.48			:: 8 8 8	0.15	0.14	0.14	2.74	2.72	273	7.69	2.59	7.64	2.46	7.65	
Antibody Dilutions 1:4000 1:8000 1:32000 1:32000 1:32000 1:128000 1:256000 1:512000 1:1 0.09 0.08 0.07 0.07 0.07 0.07 0.07 0.09 0.08 0.07 0.07 0.07 0.07 0.07 0.09 0.08 0.07 0.07 0.07 0.07 0.09 0.07 0.07 0.07 0.07 0.07 2.63 2.49 2.29 1.87 1.39 0.92 0.57 0.33 2.64 2.47 2.26 1.93 1.42 0.94 0.57 0.34 2.50 2.21 1.83 1.34 0.99 0.64 0.38 0.22 2.50 2.21 1.83 1.34 0.99 0.64 0.38 0.22 2.44 2.21 1.83 1.34 1.00 0.62 0.37 0.22 2.40 2.34 2.08 1.73 1.39 0.81 0.49 0.29 2.61 2.45 2.14 1.76 1.30 0.82 0.48 0.29	Antibody Dilutions 3000 1:16000 1:32000 1:64000 1:128000 1:256000 1:512000 0.08 0.08 0.07 0.07 0.07 0.07 0.08 0.08 0.07 0.07 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.08 0.07 0.08 0.09 0.09 0.04 0.38 0.22 0.21 1.83 1.34 0.99 0.64 0.38 0.22 0.21 1.83 1.34 0.99 0.64 0.38 0.22 0.21 1.83 1.34 1.00 0.63 0.37 0.22 0.24 0.81 1.73 1.29 0.81 0.49 0.29 0.34 0.08 1.73 1.29 0.81 0.49 0.29 0.34 0.08 1.77 1.76 1.30 0.82 0.48 0.29	Antibody Dilutions 1:32000 1:64000 1:128000 1:512000 0.07 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.08 1.87 1.39 0.92 0.57 0.34 1.93 1.42 0.94 0.57 0.34 1.34 0.99 0.64 0.57 0.34 1.34 0.99 0.64 0.38 0.22 1.34 1.00 0.62 0.37 0.22 1.34 1.00 0.63 0.37 0.22 1.34 1.00 0.63 0.37 0.22 1.73 1.29 0.81 0.49 0.29 1.76 1.30 0.82 0.48 0.29	Antibody Dilutions 1:64000 1:128000 1:512000 0.07 0.07 0.07 0.08 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 0.07 1.39 0.92 0.57 0.34 1.42 0.94 0.57 0.34 1.41 0.93 0.57 0.34 0.99 0.64 0.38 0.22 1.00 0.62 0.37 0.22 1.00 0.63 0.37 0.22 1.29 0.81 0.49 0.29 1.30 0.82 0.48 0.29	256000 1:512000 0.07 0.08 0.07 0.07 0.07 0.03 0.57 0.34 0.57 0.34 0.57 0.34 0.57 0.22 0.37 0.22 0.49 0.29 0.48 0.29	256000 1:512000 0.07 0.08 0.07 0.07 0.07 0.03 0.57 0.34 0.57 0.34 0.57 0.34 0.57 0.22 0.37 0.22 0.49 0.29 0.48 0.29	.256000 1:512000 0.07 0.08 0.07 0.03 0.07 0.33 0.57 0.34 0.57 0.34 0.57 0.34 0.57 0.22 0.37 0.22 0.49 0.29 0.48 0.29		0.07 0.07 0.07 0.07 0.20 0.21 0.15 0.15 0.19 0.19				1:20480	0.08	0.0	0.08	0.14	0.14	0.14	0.11	0.11	0,11	0.13	0.13	

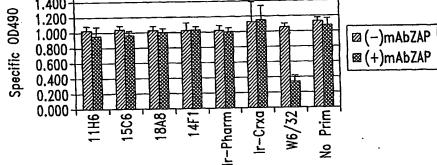
Fig. 24

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Anti-08E mAb Binding to 08E Amino Acids 61-80 Induces Ligand Internalization

Hek Internalization of OBE mAbs

1.600
1.400
1.200
1.000
1.000
1.000



Primary Ab (50ng/well)

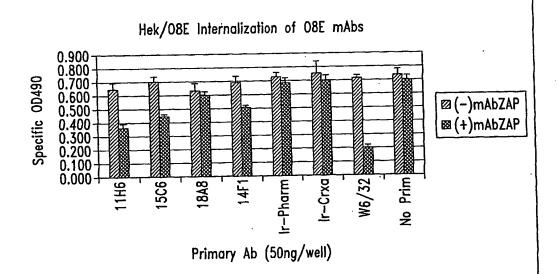


Fig. 25

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atcogggett tggcccaggg tccgatatca gcttcgtccc agttgcaggg cccggcagca 420
ttctccgagc cgagcccaat gcccattcga gctctaatct cggccctagc cttggcttca 480
gotgoagoot cagotgoago ottoaaatoo gottocatog cototoggta o
                                                                  531
<210> 7
<211> 531
<212> DNA
<213> Homo sapiens
<400> 7
gccaagaaag cccgaaaggt gaagcatctg gatggggaag aggatggcag cagtgatcag 60
agtcaggett etggaaceae aggtggeega agggteteaa aggeeetaat ggeeteaatg 120
geoegeaggg etteaagggg teceatagee ttttgggeee geagggeate aaggaetegg 180
ttggctgctt gggcccggag agccttgctc tccctgagat cacctaaagc ccgtaggggc 240
aaggetegee gtagagetge caageteeag teateceaag ageetgaage accaccacet 300
cgggatgtgg cccttttgca agggaggca aatgatttgg tgaagtacct tttggctaaa 360
gaccagacga agattcccat caagcgctcg gacatgctga aggacatcat caaagaatac 420
actgatgtgt accccgaaat cattgaacga gcaggctatt ccttggagaa ggtatttggg 480
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<210> 8
<211> 531
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 481
<223> n = A, T, C or G
<400> 8
gaggteteac tatgttgeec aggetgttet tgaaeteetg ggateaagea atecaeecat 60
gttggtctcc aaaagtgctg ggatcatagg cgtgagccac ctcacccagc caccaatttt 120
caatcaggaa gactttttcc ttcttcaaga agtgaagggt ttccagagta tagctacact 180
attgcttgcc tgagggtgac tacaaaattg cttgctaaaa ggttaggatg ggtaaagaat 240
tagattttct gaatgcaaaa ataaaatgtg aactaatgaa ctttaggtaa tacatattca 300
taaaataatt attcacatat ttcctgattt atcacagaaa taatgtatga aatgctttga 360
gtttcttgga gtaaactcca ttactcatcc caagaaacca tattataagt atcactgata 420
ataagaacaa caggaccttg tcataaattc tggataagag aaatagtctc tgggtgtttg 480
ntcttaattg ataaaattta cttgtccatc ttttagttca gaatcacaaa a
                                                                  531
<210> 9
<211> 531
<212> DNA
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<213> Homo sapiens
<220>
<221> misc_feature
<222> 528
<223> n = A, T, C \text{ or } G
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ggtgcacaga ccagcacggc tetgtgacet gtttgttaca ggtccatgat gaggtaaaca 180
atacactgag tataagggtt ggtttagaaa ctcttacagc aatttgacaa agtaatcttc 240
tgtgcagtga atctaagaaa aaaattgggg ctgtatttgt atgttccttt ttttcatttc 300
atgttctgag ttacctattt ttattgcatt ttacaaaagc atccttccat gaaggaccgg 360
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tecaeccaag gagecaggga getgggetaa accaaagaat tttgettttg gttaatcate 480
aggtacttga gttggaattg ttttaatccc atcattacca ggctggangt g
<210> 10
<211> 861
<212> DNA
 <213> Homo sapiens
<400> 10
 cegeggetee tgtccagace etgaceetee etcecaagge teaacegtee eccaacaace 60
gccagccttg tactgatgtc ggctgcgaga gcctgtgctt aagtaagaat caggccttat 120
 tggagacatt caagcaaagg ttggacaact acttttccag aacagaaagg aaactcatgc 180
 atcagaaaag gtgactaata aaggtaccag aagaatatgg ctgcacaaat accagaatct 240
 gatcagataa aacagtttaa ggaatttctg gggacctaca ataaacttac agagacctgc 300
 tttttggact gtgttagaga cttcacaaca agagaagtaa aacctgaaga gaccacctgt 360
 tcagaacatt gcttacagaa atatttaaaa atgacacaaa gaatatccat gagatttcag 420
 gaatatcata ttcagcagaa tgaagccctg gcagccaaag caggactcet tggccaacca 480
 cgatagagaa gtcctgatgg atgaactttt gatgaaagat tgccaacagc tgctttattg 540
 gaaatgagga ctcatctgat agaatcccct gaaagcagta gccaccatgt tcaaccatct 600
 gtcatgactg tttggcaaat ggaaaccgct ggagaaacaa aattgctatt taccaggaat 660
 aatcacaata gaaggtetta ttgttcagtg aaataataag atgcaacatt tgttgaggec 720
 ttatgattca gcagcttggt cacttgatta gaaaaataaa ccattgtttc ttcaattgtg 780
 actgttaatt ttaaagcaac ttatgtgttc gatcatgtat gagatagaaa aatttttatt 840
 actcaaagta aaataaatgg a
 <210> 11
 <211> 541
 <212> DNA
 <213> Homo sapiens
  <400> 11
  gaaaaaaaat ataaaacaca cttttgcgaa aacggtggcc ctaaaagagg aaaagaattt 60
  caccaatata aatccaattt tatgaaaact gacaatttaa tccaagaatc acttttgtaa 120
  atgaagctag caagtgatga tatgataaaa taaacgtgga ggaaataaaa acacaagact 180
  tggcataaga tatatccact tttgatatta aacttgtgaa gcatattctt cgacaaattg 240
  tgaaagcgtt cctgatcttg cttgttctcc atttcaaata aggaggcata tcacatccca 300
  agagtaacag aaaaagaaaa aagacatttt tgcattttga gatgaaccaa agacacaaaa 360
  caaaacgaac aaagtgtcat gtctaattct agcctctgaa ataaaccttg aacatctcct 420
  acaaggcacc gtgatttttg taattctaac ctgaagaaat gtgatgactt ttgtggacat 480
  gaaaatcaga tgagaaaact gtggtctttc caaagcctga actcccctga aaacctttgc 540
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<211> 541
<212> DNA
<213> Homo sapiens
<400> 12
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catectette tqtacaqtqc tqccqqqtac aacqqctate tttqtettta teetqaqatq 120
aagatgatgc ttctgtttct cctaccataa ctgaagaaat ttcgctggaa gtcgtttgac 180
tggctgtttc tctgacttca ccttctttgt caaacctgag tctttttacc tcatgcccct 240
cagettecae ageatettea tetggatgtt tattttteaa agggeteaet gaggaaaett 300
ctgattcaga ggtcgaagag tcactgtgat ttttctcctc attttqctqc aaatttgcct 360
ctttgctgtc tgtgctctca ggcaacccat ttgttgtcat gggggctgac aaagaaacct 420
ttggtcgatt aagtggcctg ggtgtcccag qcccatttat attagacctc tcagtatagc 480
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<210> 13
<211> 441
<212> DNA
<213> Homo sapiens
<400> 13
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ettecceegg etecettegt ttecceecee eggtegeetg egtgeeggag tgtgtgegag 120
ggagggggag ggcgtcgggg gggtgggggg aggcgttccg gtccccaaga gacccgcgga 180
gggaggcgga ggctgtgagg gactccggga agccatggac gtcgagaggc tccaggaggc 240
gctgaaagat tttgagaaga gggggaaaaa ggaagtttgt cctgtcctgg atcagtttct 300
ttgtcatgta gccaagactg gagaaacaat gattcagtqq tcccaattta aaqqctattt 360
tattttcaaa ctggagaaag tgatggatga tttcagaact tcagctcctg agccaagagg 420
tcctcccaac cctaatgtcg a
<210> 14
<211> 131
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 126
<223> n = A,T,C or G
<400> 14
aagcaggegg etceegeget egcaggeeg tgecacetge eegceegeee getegetege 60
tegecegeeg egeegeetg eegacegeea geatgetgee gagagtggge tgeecegege 120
tgccgntgcc g
                                                                   131
<210> 15
<211> 692
<212> DNA
<213> Homo sapiens
<400> 15
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tcaaagtttg caaaaacgtg aagattaact taattgtcaa atattcctca ttgccccaaa 120
tcagtatttt ttttatttct atgcaaaagt atgccttcaa actgcttaaa tgatatatga 180
tatgatacac aaaccagttt tcaaatagta aagccagtca tcttgcaatt gtaagaaata 240
ggtaaaagat tataagacac cttacacaca cacacacaca cacacagtg tgcacgccaa 300
tgacaaaaaa caatttggcc tctcctaaaa taagaacatg aagaccctta attgctgcca 360
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ggagggaaca ctgtgtcacc cctccctaca atccaggtag tttcctttaa tccaatagca 420
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atteatgtcc acceaetggt gccctgaaaa aatgccaata attttteget eccaettetg 540
ctgctgtctc ttccacatcc tcacatagac cccagacccg ctggcccctg gctgggcatc 600
gcattgctgg tagagcaagt cataggtctc gtctttgacg tcacagaagc gatacaccaa 660
attgcctggt cggtcattgt cataaccaga ga
<210> 16
<211> 728
<212> DNA
<213> Homo sapiens
<400> 16
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tgatggtttc ataaggettt teeecetttt geteageact teteetteet geegecatgt 180
gaagaaggac atgtttgctt ccccttccac cacgattgta agttgtttcc tgaggcctcc 240
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agaggattet teetggatee cageaettee tetgaatget actgacatte ttettgagga 420
ctttaaactg ggagatagaa aacagattcc atggctcagc agcctgagag cagggaggga 480
gccaagctat agatgacatg ggcagcctcc cctgaggcca ggtgtggccg aacctgggca 540
gtgctgccac ccaccccacc agggccaagt cctgtccttg gagagccaag cctcaatcac 600
tgctagcctc aagtgtcccc aagccacagt ggctaggggg actcagggaa cagttcccag 660
tetgecetae ttetettace tttacecete atacetecaa agtagaceat gtteatgagg 720
 tccaaagg
 <210> 17
 <211> 531
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> 518, 528
 <223> n = A, T, C or G
 <400> 17
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 aacgcgaaga acaggagcgg aagctgcagg ctgaaaggga caagcgaatg cgagaggagc 120
 agetggeeeg ggaggetgaa geeegggetg aacgtgagge egaggegegg agaegggagg 180
 agcaggaggc tcgagagaag gcgcaggctg agcaggagga gcaggagcga ctgcagaagc 240
 agaaagaga agccgaagcc cggtcccggg aagaagctga gcgccagcgc caggagcggg 300
 aaaagcactt tcagaaggag gaacaggaga gacaagagcg aagaaagcgg ctggaggaga 360
 taatgaagag gactcggaaa tcagaagccg ccgaaaccaa gaagcaggat gcaaaggaga 420
 ccgcagctaa caattccggc ccagaccctt gtgaaagctg tagagactcg gecetctggg 480
 cttccagaaa ggattctatt gcagaaagga aggagctngg ccccccangg a
 <210> 18
 <211> 1041
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc feature
  <222> 544
  <223> n = A,T,C or G
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<400> 18
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agtgctgggt ctgattactg caacacagag aacqaagaag aacttttcct catacaggat 120
cagcagggcc tcatcacact gggctggatt catactcacc ccacacagac cgcgtttctc 180
tecagtgteg acctacacae teaetgetet taccagatga tgttgccaga gtcagtagee 240
attgtttgct cccccaagtt ccaggaaact ggattcttta aactaactga ccatggacta 300
gaggagattt cttcctgtcg ccagaaagga tttcatccac acagcaagga tccacctctg 360
ttetgtaget geagecaegt gaetgttgtg gaeagageag tgaecateae agaeettega 420
tgagcgtttg agtccaacac cttccaagaa caacaaaacc atatcagtgt actgtagccc 480
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cacntgagaa agagctgatt ttgtatttca ggtttgaaaa gaaataactg aacatatttt 600
ttaggcaagt cagaaagaga acatggtcac ccaaaagcaa ctgtaactca gaaattaagt 660
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agettattac tggggtgagg gacagettac tecatttgac cagattgttt ggctaacaca 960
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<210> 19
<211> 1043
<212> DNA
<213> Homo sapiens
<400> 19
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cagcagggcc tcatcacact gggctggatt catactcacc ccacacagac cgcgtttctc 180
tocagtgtcg acctacacac tcactgctct taccagatga tgttgccaga gtcagtagcc 240
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gaggagattt cttcctgtcg ccagaaagga tttcatccac acagcaagga tccacctctq 360
ttctgtagct gcagccacgt gactgttgtg gacagagcag tgaccatcac agaccttcga 420
tgagcgtttg agtccaacac cttccaagaa caacaaaacc atatcagtgt actgtagccc 480
cttaatttaa gctttctaga aagctttgga agtttttgta gatagtagaa aggggggcat 540
cacctgagaa agagctgatt ttgtatttca ggtttgaaaa gaaataactg aacatatttt 600
ttaggcaagt cagaaagaga acatggtcac ccaaaagcaa ctgtaactca gaaattaagt 660
tactcagaaa ttaagtagct cagaaattaa gaaagaatgg tataatgaac ccccatatac 720
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agettattac tggggtgagg gacagettac tecatttgac cagattgttt ggctaacaca 960
tcccgaagaa tgattttgtc aggaattatt gttatttaat aaatatttca ggatattttt 1020
cctctacaat aaagtaacaa tta
<210> 20
<211> 448
<212> DNA
<213> Homo sapiens
<400> 20
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ggaacaggga aggtgaaagt tggagtgaga tgtcttccat atctatacct ttgtgcacag 120
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ggaactggtg ggaggtcaag tggggaagtt ggtgaatgtg gaataactta cctttgtgct 240
ccacttaaac cagatgtgtt gcagctttcc tgacatgcaa ggatctactt taattccaca 300
ctctcattaa taaattgaat aaaagggaat gttttggcac ctgatataat ctgccaggct 360
atgtgacagt aggaaggaat ggtttcccct aacaagccca atgcactggt ctgactttat 420
```

```
448
aaattattta ataaaatgaa ctattatc
<210> 21
<211> 411
<212> DNA
<213> Homo sapiens
<400> 21
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qaaqaqaca cccaqtqttq ggctgaaaac atctgaaagt agggagaaga acctaaaata 120
atcagtatet cagagggete taaggtgeea agaagtetea etggacattt aagtgeeaac 180
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aagtgagact caagagtcta ctgctttagt ggcaactaca gaaaactggt gttacccaga 300
aaaacaggag caattagaaa tggttccaat atttcaaagc tccgcaaaca ggatgtgctt 360
teetttgeee atttagggtt tettetettt cetttetett tattaaccae t
<210> 22
<211> 896
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 230, 320
<223> n = A, T, C or G
<400> 22
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quateteaac caccageete tgtggggggc aggtgggegt ecetgtgggc etetgggece 120
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 gaccagetea ateteettgt eceggeettt eeggatttet teeeteaget eetgtteeeg 780
 qttcaqcage cacgeeteet cetteetggt geggeeggee teccaegeet geeteteeag 840
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 <210> 23
 <211> 111
 <212> DNA
 <213> Homo sapiens
 <400> 23
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 attttcctag tggtttgact ttaaaaaataa ataaggttta attttctccc c
 <210> 24
 <211> 531
 <212> DNA
 <213> Homo sapiens
 <220>
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<221> misc feature
<222> 472, 494
<223> n = A, T, C \text{ or } G
<400> 24
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ggctggagtg caatggtgtg atcttggctc actgcaacct ccacctcctg ggttcaagcg 120
attetectge cacageetee egagtagetg ggattacagg tgeeegeeae cacaeecage 180
taatttttat atttttagta aagacagggt ttccccatgt tggccaggct ggtcttgaac 240
ttctgacctc aggtgatcca cctgcctcgg cctcccaaag tgttgggatt acaggcgtga 300
getaccegtg cetggecage caetggagtt taaaggacag teatgttgge tecageetaa 360
ggcggcattt tcccccatca gaaagcccgc ggctcctgta cctcaaaata gggcacctgt 420
aaagtcagtc agtgaagtct ctgctctaac tggccacccg gggccattgg cntctgacac 480
agcettgeca ggangeetge atetgeaaaa gaaaagttea etteetttee g
<210> 25
<211> 471
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 377
<223> n = A, T, C or G
<400> 25
cagagaatct kagaaagatg tcgcgttttc ttttaatgaa tgagagaagc ccatttgtat 60
ccctgaatca ttgagaaaag gcggcggtgg cgacagcggc gacctaggga tcgatctgga 120
gggacttggg gagcgtgcag agacctctag ctcgagcgcg agggacctcc cgccgggatg 180
cctggggagc agatggaccc tactggaagt cagttggatt cagatttctc tcagcaagat 240
actocttgcc tgataattga agattctcag cctgaaagcc aggttctaga ggatgattct 300
ggtteteact teagtatget atetegacae ettectaate teeagacgea caaagaaaat 360
cctgtgttgg atgttgngtc caatccttga acaaacagct ggagaagaac gaggagaccg 420
gtaatagtgg gttcaatgaa catttgaaag aaaaccaggt tgcagaccct g
<210> 26
<211> 541
<212> DNA
<213> Homo sapiens
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gagtggaagc caaagaacac ccaccttcct cccttgaagg agtagagcaa ccatcagaag 120
atactgtttt attgctctgg tcaaacaagt cttcctgagt tgacaaaacc tcaggctctg 180
gtgacttctg aatctgcagt ccactttcca taagttcttg tgcagacaac tgttcttttg 240
cttccatagc agcaacagat gctttggggc taaaaggcat gtcctctgac cttgcaggtg 300
gtggattttg ctcttttaca acatgtacat ccttactggg ctgtgctgtc acagggatgt 360
cettgetgga etgttetget atggggatat ettegttgga etgttettea tgettaattg 420
cagtattagc atccacatca gacagcctgg tataaccaga gttggtggtt actgattgta 480
gctgctcttt gtccacttca tatggcacaa gtattttcct caacatcctg gctctgggaa 540
<210> 27
<211> 461
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
<222> 367
<223> n = A,T,C or G
<400> 27
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agtgtgggaa gggggctgga aacaaagtat tetttteett caaagettea tteetcaagg 180
cctcaattca agcagtcatt gtccttgctt tcaaaagtct gtgtgtgctt catggaaggt 240
atatgtttgt tgccttaatt tgaattgtgg ccaggaaggg tctggagatc taaattcaga 300
gtaagaaaac ctgagctaga actcaggcat ttctcttaca gaacttggct tgcagggtag 360
aatgaangga aagaaactta gaagctcaac aagctgaaga taatcccatc aggcatttcc 420
cataggeett geaactetgt teactgagag atgttateet g
<210> 28
<211> 541
<212> DNA
<213> Homo sapiens
<400> 28
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<212> DNA
<213> Homo sapiens
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<222> 18
<223> n = A, T, C or G
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geogeogeog etgetgeege tgetgeeget getgetgetg e
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<210> 36
<211> 341
<212> DNA
<213> Homo sapiens
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ctattattag cagtgaggag cagaagcagc tgatgctgta ctatcacaga agacaagagg 180
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 tgttgttgtt gatgatgatg atgatgatga taatatttt ctatccccag tgcacaactg 180
 cttgaaccta ttagataatc aatacatgtt tcttgaactg agatcaattt ccccatgttg 240
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<400> 38
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 <213> Homo sapiens
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<211> 461
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<213> Homo sapiens
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<222> 128
<223> n = A, T, C or G
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<212> DNA
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gggctccaac ttgcagacgg cctgttgtgg gacagtctct gtaatcgcga aagcaaccat 120
ggaagacctg ggggaaaaca ccatggtttt atccaccctg agatctttga acaacttcat 180
ctctcagcgt gcggagggag gctctggact ggatatttct acctcggccg cgaccacqct 240
<210> 76
<211> 330
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 288
<223> n = A, T, C or G
<400> 76
tagegyggtc geggeegagg yetgettytc tgtccagecc agggeetgtg gggtcaggge 60
ggtgggtgca gatggcatcc actccggtgg cttccccatc tttctctggc ctgagcaagg 120
tcagcctgca gccagagtac agagggccaa cactggtgtt cttgaacaag ggccttagca 180
ggccctgaag grccctctct gtagtgttga acttcctgga gccaggccac atgttctcct 240
cataccgcag gytagygatg gtgaagttga gggtgaaata gtattmangr agatggctgg 300
caracetgee egggeggeeg etesaaatee
<210> 77
<211> 361
<212> DNA
<213> Homo sapiens
<400> 77
agcgtggtcg cggccgaggt gtccttcagg gtctgcttat gcccttgttc aagaacacca 60
gtgtcagetc tetgtaetct ggttgcagae tgacettgct caggeetgag aaggatgggg 120
cagecaceag agtggatget gtetgeacee ategteetga ceceaaaage cetggaetgg 180
acagagageg getgtaetgg aagetgagee agetgaeeca eggeateaet gagetgggee 240
ectacaccct ggacagggac agtetetatg teaatggttt cacccategg agetetgtac 300
ccaccaccag caccggggtg gtcagcgagg agccattcaa cctgcccggg cggccgctcg 360
                                                                   361
<210> 78
<211> 356
<212> DNA
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<213> Homo sapiens
<220>
<221> misc_feature
<222> 7, 346, 350, 353
<223> n = A,T,C or G
<400> 78
ttggggnttt mgagcggccg cccgggcagg taccggggtg gtcagcgagg agccattcac 60
actgaacttc accatcaaca acctgcggta tgaggagaac atgcagcacc ctggctccag 120
gaagttcaac accacggaga gggtccttca gggcctgctc aggtccctgt tcaagagcac 180
caqtqttqqc cctctqtact ctqqctqcaq actqactttq ctcaqacttq aqaaacatgg 240
ggcagccact ggagtggacg ccatctgcac cctccgcctt gatcccactg gtcctggact 300
ggacagagag cggctatact gggagctgag ccagtcctct ggcggngacn ccnctt
<210> 79
<211> 226
<212> DNA
<213> Homo sapiens
<400> 79
agcgtggtcg cggccgaggt ccagtcgcag catgctcttt ctcctgccca ctggcacagt 60
gaggaagatc tctgctgtca gtgagaaggc tgtcatccac tgagatggca gtcaaaagtg 120
catttaatac acctaacgta tcgaacatca tagcttggcc caggttatct catatgtgct 180
cagaacactt acaatagcct gcagacctgc ccgggcggcc gctcga
<210> 80
<211> 444
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 23
<223> n = A, T, C or G
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gatggtgaag ttgagggtga atggtaccag gagagggcca gcagccataa ttgtsgrgck 120
gsmgmssgag gmwggwgtyy cwgaggttcy rarrtccact gtggaggtcc caggagtgct 180
ggtggtgggc acagagstcy gatgggtgaa accattgaca tagagactgt tcctgtccag 240
ggtgtagggg cccagctctt yratgycatt ggycagttkg ctyagctccc agtacagccr 300
ctctckgyyg mgwccagsgc ttttggggtc aagatgatgg atgcagatgg catccactcc 360
agtggctgct ccatccttct cggacctgag agaggtcagt ctgcagccag agtacagagg 420
gccaacactg gtgttctttg aata
<210> 81
<211> 310
<212> DNA
<213> Homo sapiens
<400> 81
tegageggee geeegggeag gteaggaage acattggtet tagageeact geeteetgga 60
ttccacctqt gctqcqqaca tctccagqqa qtqcaqaaqq qaaqcaqqtc aaactqctca 120
gatcagtcag actggctgtt ctcagttctc acctgagcaa ggtcagtctg cagccagagt 180
acagagggcc aacactggtg ttcttgaaca agggcttgag cagaccctgc agaaccctct 240
tccgtggtgt tgaacttcct ggaaaccagg gtgttgcatg tttttcctca taatgcaagg 300
ttggtgatgg
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26

```
<210> 82
<211> 571
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 202
<223> n = A, T, C or G
<400> 82
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tacaaatgga atttcatctt gtttccatgc tgagtagtga aacagtgaca aagctaatca 120
taataaccta catcaaaaga gaactaagct aacactgctc actttcttt taacaggcaa 180
aatataaata tatgcactct anaatgcaca atggtttagt cactaaaaaa ttcaaatggg 240
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tgtttaaggg ttcctggcac tgcatctctt ggccactagc tgaatcttga catggaaggt 360
tttagctaat qccaaqtqqa qatqcagaaa atqctaagtt gacttagggg ctgtgcacag 420
gaactaaaag gcaggaaagt actaaatatt gctgagagca tccaccccag gaaggacttt 480
accttccagg agctccaaac tggcaccacc cccagtgctc acatggctga ctttatcctc 540
cgtgttccat ttggcacagc aagtggcagt g
<210> 83
<211> 551
<212> DNA
<213> Homo sapiens
<400> 83
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aaqqqaaaaq atqcttctqq qaacaaqqtt aaaqccqaqc cagccaaaat aqaaqctttc 120
cgagcttcac tttccaagct aggggatgtc tatgtcaatg atgcttttgg cactgctcac 180
agageceaca getecatggt aggagteaat etgecacaga aggetggtgg gtttttgatg 240
aagaaggagc tgaactactt tgcaaaggcc ttggagagcc cagagcgacc cttcctggcc 300
atcctgggcg gagctaaagt tgcagacaag atccagctca tcaataatat gctggacaaa 360
gtcaatgaga tgattattgg tggtggaatg gcttttacct tccttaaggt gctcaacaac 420
atggagattg gcacttctct gtttgatgaa gagggagcca agattgtcaa agacctaatg 480
tccaaagctg agaagaatgg tgtgaagatt accttgcctg ttgactttgt cactgctgac 540
aagtttgatg a
<210> 84
<211> 571
<212> DNA
<213> Homo sapiens
<400> 84
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taaqttotqa ttocaactta qotaattoat totqaqaact gtggtatagg tggcgtgtot 120
cttctagctg ggacaaaagt tctttgtttt ccccctgtag agtatcacag accttctgct 180
gaagctggac ctctgtctgg gccttggact cccaaatctg cttgtcatgt tcaagcctgg 240
aaatgttaat ctttaattct teeatatgga tggacatetg tetaagttga teetttagaa 300
cactgcaatt atcttctttg agtctaattt cttcttcttt gctttgaatc gcatcactaa 360
acttectete ceatttetta getteateta teaccetgte aegateatee tggagggaag 420
acatgetett agtaaagget geaagetggg teacagtact gtecaagttt teetgaagtt 480
gctgaactte cttgtctttc ttgttcaaag taacctgaat ctctccaatt gtctcttcca 540
                                                                   571
agtggacttt ttctctgcgc aaagcatcca g
```

<210> 85

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<211> 561
<212> DNA
<213> Homo sapiens
<400> 85
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aatcaaagga ttcagcatgt ggtggaagct gtgaggcaag agaaacaaga actgtatggc 120
aagttaagaa gcacagaggc aaacaagaag gagacagaaa agcagttgca ggaagctgag 180
caagaaatgg aggaaatgaa agaaaagatg agaaagtttg ctaaatctaa acagcagaaa 240
atcctagagc tggaagaaga gaatgaccgg cttagggcag aggtgcaccc tgcaggagat 300
acagetaaag agtgtatgga aacaettett tetteeaatg ceageatgaa ggaagaactt 360
gaaagggtca aaatggagta tgaaaccctt tctaagaagt ttcagtcttt aatgtctgag 420
aaagactctc taagtgaaga ggttcaagat ttaaagcatc agatagaagg taatgtatct 480
aaacaagcta acctagaggc caccgagaaa catgataacc aaacgaatgt cactgaagag 540
ggaacacagt ctataccagg t
                                                                   561
<210> 86
<211> 795
<212> DNA
<213> Homo sapiens
<400> 86
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aatteteace gttacaacaa eeccatgagg tatttattee cattetatag atagggaaac 120
cacageteaa gtaagttagg aaactgagee aagtatacac agaataegaa gtggcaaaac 180
tagaaggaaa gactgacact gctatctgct ggcctccagt gtcctggctc ttttcacacg 240
qqttcaatqt ctccaqcqct qctqctqctq ctqcattacc atqccctcat tqtttttctt 300
cctctqqtqt tcaactqcat ccttcaaaqa atctaactca ttccaqaqac cacttatttc 360
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ttggtagttt tgttgtttaa gctgctcaat ttgggactta aacaatttgt tttcatcttg 480
tacatcctgt aacagctgtg ttttgctaga aagatcactc tccctcttt ttagcatggc 540
ttctaacctc ttcaattcat tttccttttc tttcaacaca atctcaagtt cttcaaactg 600
tgatgcagaa gaggcctctt tcaagttatg ttgtgctact tcctgaacat gtgcttttaa 660
agatteattt tettettgaa gateetgtaa eeaetteeet gtattggeta ggtetttete 720
tttctcttcc aaaacagcct tcatggtatt catctgttcc tcttttcctt ttaataagtt 780
caggagette agaac
                                                                   795
<210> 87
<211> 594
<212> DNA
<213> Homo sapiens
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caactgggtt tatgtcttca tattttatat ttttgtaaat taaaaaaatt acaagtttta 120
aatagecaat ggetggttat atttteagaa aacatgatta gaetaattea ttaatggtgg 180
cttcaagett ttccttattg getceagaaa attcacceae ettttgteee ttcttaaaaa 240
actggaatgt tggcatgcat ttgacttcac actctgaagc aacatcctga cagtcatcca 300
catctactic aaggaatatc acgitggaat actiticaga gagggaatga aagaaaggct 360
tgatcatttt gcaaggccca caccacgtgg ctgagaagtc aactactaca agtttatcac 420
ctgcagcgtc caaggettee tgaaaageag tettgetete gatetgette accatettgg 480
ctgctggagt ctgacgagcg gctgtaagga ccgatggaaa tggatccaaa gcaccaaaca 540
gagetteaag actegetget tggettgaat teggateega tategeeatg geet
<210> 88
<211> 557
<212> DNA
<213> Homo sapiens
```

```
<400> 88
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tttatatttt tgtaaattaa aaaaattmca agttttaaat agccaatggc tggttatatt 120
ttcagaaaac atgattagac taattcatta atggtggctt caagcttttc cttattggct 180
ccagaaaatt cacccacctt ttgtcccttc ttaaaaaact ggaatgttgg catgcatttg 240
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ttggaatact tttcagagag ggaatgaaag aaaggcttga tcattttgca aggcccacac 360
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aaagcagtct tgctctcgat ctgcttcacc atcttggctg ctggagtctg acgagcggct 480
gtaaggaccg atggaaatgg atccaaagca ccaaacagag cttcaagact cgctgcttgg 540
catgaattcg gatccga
<210> 89
<211> 561
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 544, 551
\langle 223 \rangle n = A, T, C or G
<400> 89
tacaaacttt attgaaacgc acacgcgcac acacacaaac acccctgtgg atagggaaaa 60
gcacctggcc acagggtcca ctgaaacggg gaggggatgg cagcttgtaa tgtggctttt 120
gccacaaccc cettetgaca gggaaggeet tagattgagg ceceacetee catggtgatg 180
gggageteag aatggggtee agggagaatt tggttagggg gaggtgetag ggaggeatga 240
gcagagggca ccctccgagt ggggtcccga gggctgcaga gtcttcagta ctgtccctca 300
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caaacacttg gtacccctgg ctgcgcagcg gaagccagca ggacagcagt ggcgccgatc 420
agcacaacag acgccctggc ggtagggaca gcaggcccag ccctgtcggt tgtctcggca 480
gcaggtetgg ttatcatggc agaagtgtcc ttcccacact tcacgtcctt cacacccacg 540
tganggetac nggecaggaa g
<210> 90
<211> 561
<212> DNA
<213> Homo sapiens
<400> 90
cccgtgggtg ccatccacgg agttgttacc tgatctttgg aagcaggatc gcccgtctgc 60
actgcagtgg aagccccgtg ggcagcagtg atggccatcc ccgcatgcca cggcctctgg 120
gaaggggcag caactggaag tccctgagac ggtaaagatg caggagtggc cggcagagca 180
gtgggcatca acetggcagg ggccacccag atgcctgctc agtgttgtgg gccatttgtc 240
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tgctgctccg atcacctgca ctgctgcccc aagacactgt gtgtgacctg atccagagta 540
agtgcctctc caaggagaac g
<210> 91
<211> 541
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 480, 491
<223> n = A, T, C or G
<400> 91
gaatcacctt tctggtttag ctagtacttt gtacagaaca atgaggtttc ccacagcgga 60
qtctccctgq qctctgtttg gctctcggta aggcaggcct acaccttttc ctctcctcta 120
tggagagggg aatatgcatt aaggtgaaaa qtcaccttcc aaaagtgaga aagggattcg 180
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tctccgggaa gaggcagaga cagtttggcg aaaaagacac agggaaggag ggggtggtga 420
aaggagaaag cagcetteca gttaaagate agceeteagt taaaggteag etteeegean 480
gctggcctca ngcggagtct gggtcagagg gaggagcagc agcagggtgg gactggggcg 540
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t
<210> 92
<211> 551
<212> DNA
<213> Homo sapiens
<400> 92
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gtqaagcgca agatccaggt tctgcagcag caggcagatg atgcagagga gcgagctgag 120
cgcctccagc gagaagttga gggagaaagg cgggcccggg aacaggctga ggctgaggtg 180
gcctccttga accgtaggat ccagctggtt gaagaagagc tggaccgtgc tcaggagcgc 240
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gcagagtccc gttgccgaga gatggatgag cagattagac tgatggacca gaacctgaag 540
tgtctgagtg c
<210> 93
<211> 531
<212> DNA
<213> Homo sapiens
<400> 93
gagaacttgg cetttattgt gggcccagga gggcacaaag gtcaggaggc ccaagggagg 60
gatetggttt tetggatage eaggteatag eatgggtate agtaggaate egetgtaget 120
gcacaggect cacttgctgc agttccgggg agaacacctg cactgcatgg cgttgatgac 180
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teccaetttg atgtactgea cettggetgt gatgtetttg caatcagget ceteacatgt 420
gtcacagcag gtgcctggaa ttttcacgat tttgcctcct tcagccagac acttgtgttc 480
atcaaatggt gggcagcccg tgaccctctt ctcccagatg tactctcctc t
<210> 94
<211> 531
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 517
<223> n = A, T, C or G
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<400> 94
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ctgcagagtc atcgtgtcaa ttgtgaccat ggaccccggc cttcatgtgc caacagccag 120
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ccgtacgttg gtgaaaacat ggaagtcagc atctacggcg ctatcatgta tgaagtcagg 480
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<210> 95
<211> 605
<212> DNA
<213> Homo sapiens
<400> 95
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aggaggratg cetteettgt cytggatett tgcyttgaer tteteratgg tgteaetegg 540
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tctaa
<210> 96
<211> 531
<212> DNA
<213> Homo sapiens
<400> 96
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gaggaggtga agcatctcaa acataatctc gaaaaagtgg aaggagaaag aaaagaggct 180
caagacatgc ttaatcactc agaaaaggaa aagaataatt tagagataga tttaaactac 240
aaacttaaat cattacaaca acggttagaa caagaggtaa atgaacacaa agtaaccaaa 300
getegtttaa etgacaaaca teaatetatt gaagaggeaa agtetgtgge aatgtgtgag 360
atggaaaaaa agctgaaaga agaaagagaa gctcgagaga aggctgaaaa tcggggttgtt 420
cagattgaga aacagtgttc catgctagac gttgatctga agcaatctca gcagaaacta 480
gaacatttga ctggaaataa agaaaggatg gaggatgaag ttaagaatct a
<210> 97
<211> 1017
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 963, 995, 1001, 1008, 1010
<223> n = A, T, C or G
<400> 97
egectecace atgtecatea gggtgaceca gaagtectae aaggtgteca eetetggeee 60
```

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cttctcccga gtgggcagca gcaactttcg cggtggcctg ggcggcggct atggtggggc 180
cageggeatg ggaggeatca eegeagttac ggteaaceag ageetgetga geeceettgt 240
cctggaggtg gaccccaaca tccaggccgt gcgcacccag gagaaggagc agatcaagac 300
cctcaacaac aagtttgcct ccttcataga caaggtacgg ttcctggagc agcagaacaa 360
gatgctggag accaagtgga gcctcctgca gcagcagaag acggctcgaa gcaacatgga 420
caacatgttc gagagctaca tcaacarcct taggcggcag ctggagactc tgggccagga 480
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caagtatgag gatgagatca ataagcgtac agagatggag aacgaatttg tcctcatcaa 600
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<210> 98
<211> 561
<212> DNA
<213> Homo sapiens
<400> 98
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<212> DNA
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<213> Homo sapiens
<400> 108
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<210> 110
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<212> DNA
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<213> Homo sapiens
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<211> 568
<212> DNA
<213> Homo sapiens
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<213> Homo sapiens
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<210> 117
<211> 451
<212> DNA
<213> Homo sapiens
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<222> 320
<223> n = A, T, C or G
<400> 117
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<212> DNA
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<211> 391
<212> DNA
<213> Homo sapiens
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<213> Homo sapiens
<220>
<221> misc feature
<222> 409
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<210> 121
<211> 206
<212> DNA
<213> Homo sapiens
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<210> 122
<211> 131
<212> DNA
<213> Homo sapiens
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gaaaagttaa a
<210> 123
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 166, 202, 222, 225
<223> n = A, T, C or G
<400> 123
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<210> 124
 <211> 521
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 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 284, 412, 513
 <223> n = A, T, C \text{ or } G
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 acaatttaat ggagcttttg atcatgatta atgcctgcaa gattgcttca gccagccggg 360
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 <212> DNA
 <213> Homo sapiens
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<221> misc_feature
<222> 277
<223> n = A,T,C or G
<400> 125
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gtaccccage teceegacea caaccccett ceteeceegg ggaaageaag aaggageagg 120
tgtggcatct gcagctggga agagagagc cggggaggtg ccgagctcgg tgctggtctc 180
tttccaaata taaatacgtg tgtcagaact ggaaaatcct ccagcaccca ccacccaagc 240
actetecqtt ttetqeeqqt qtttqqaqaq qqqeqqnqqq caqqqqeqee aggeaecqqe 300
tggctqcggt ctactgcatc cgctgggtgt gcaccccgcg a
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<210> 126
<211> 521
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> 353, 399, 455
<223> n = A, T, C or G
<400> 126
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caggeccaga gtggcactgg acagaccatg caggtgatgc agcagatcat cactaacaca 120
ggagagatec ageagatece gqtgeagetg aatgeeggee agetgeagta tateegetta 180
gcccagcctg tatcaggcac tcaagttgtg cagggacaga tccagacact tgccaccaat 240
geteaacaga ttacacagac agaggtecag caaggacage ageagtteaa gecagtteac 300
aagatggaca gcagctctac cagatccagc aagtcaccat gcctgcgggc cangacctcg 360
ccagcccatg ttcatccagt caagccaacc agcccttcna cgggcaggcc ccccaggtga 420
ccggcgactg aagggcctga gctggcaagg ccaangacac ccaacacaat ttttgccata 480
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                                                                   521
<210> 127
<211> 351
<212> DNA
<213> Homo sapiens
<400> 127
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gtccctggga gaaaagagtg tggcaatgaa tccacccact ctccacaggg aataaatctg 180
tctcttaaat gcaaagaatg tttccatggc ctctggatgc aaatacacag agctctgggg 240
tcagagcaag ggatggggag aggaccacga gtgaaaaagc agctacacac attcacctaa 300
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<210> 128
<211> 521
<212> DNA
<213>. Homo sapiens
<400> 128
tecagacatg etectqteet aggegggag cagqaaccag acetgetatg ggaagcagaa 60.
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taaatatact aatagctaag tcatttgcca gccaggtccc ggtgaacagt agagaacaag 180
gagettgeta agaattaatt ttgetgtttt teaccecatt caaacagage tgeectgtte 240
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cctgatggag ttccattcct gccagggcac ggctgagtaa cacgaagcca ttcaagaaag 300
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gcgctactta ataaatatat ttatactttg aaattatgat aaccgatttt tcccatgcgg 420
catcctaagg gcacttgcca gctcttatcc ggacagtcaa gcactgttgt tggacaacag 480
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<212> DNA
<213> Homo sapiens
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agagcaatta atgaagctta actcaggcct gggacagttg atcttgaaag aagagatgga 180
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caacagaggg ccgaaaccaa atctcagaga ggtggacaga a
<210> 130
<211> 270
<212> DNA
<213> Homo sapiens
<400> 130
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 cttggtgaat acagtctcct tccagaggtc gggggtcagg tagctgtagg tcttagaaat 180
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 gtagcagtca tcgataccag ccatcatgag
 <210> 131
 <211> 341
 <212> DNA
 <213> Homo sapiens
 <400> 131
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 ttatgtataa tagctcatgc atgtgtccat gtcataactg tcttcatacg cttctgcact 180
 ctggggaaga aggagtacat tgaagggaga ttggcaccta gtggctggga gcttgccagg 240
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 <211> 844
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 37
 <223> n = A, T, C or G
 <400> 132
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gccatgtgga acatgagggg ctgcctgagc ccctcaccct gagatggggc aaggaggagc 180
ctccttcatc caccaagact aacacagtaa tcattgctgt tccggttgtc cttggagctg 240
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aaggaggga ctatgctctg gctccaggct cccagagctc tgatatgtct ctcccagatt 360
qtaaaqtqtq aaqacaqctq cctqqtqtqq acttqqtqac agacaatqtc ttcacacatc 420
tcctgtgaca tccagagacc tcagttctct ttagtcaagt gtctgatgtt ccctgtgagt 480
etgegggete aaagtgaaga actgtggage ceagteeace cetgeacace aggaceetat 540
ccctgcactg ccctgtgttc ccttccacag ccaaccttgc tgctccagcc aaacattggt 600
ggacatetge ageetgteag etecatgeta ecetgacett caacteetca ettecacaet 660
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aaqqtcctqa gttcaaatcc cagcaaccac atggtggctc acaaccatct gtaatggqat 780
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<211> 601
<212> DNA
<213> Homo sapiens
<400> 133
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cagoogotog toagactoca goagocaaga tggtgaagca gatogagago aagactgott 180
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acgtgatatt ccttgaagta gatgtggatg actgtcagga tgttgcttca gagtgtgaag 360
tcaaatgcat gccaacattc cagtttttta agaagggaca aaaggtgggt gaattttctg 420
qaqccaataa qqaaaaqctt qaaqccacca ttaatqaatt aqtctaatca tqttttctqa 480
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aatatgaaga cataaacccm gttgccatct gcgtgacaat aaaacattaa tgctaacact 600
                                                                  601
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<211> 421
<212> DNA
<213> Homo sapiens
<400> 134
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gigattaggt taatattgcc ttcttacaaa atttctattt taaaaaaaat tataaccttg 240
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tccctcacag caccgtttta tatatagcag agaataatga agagattgct agtctagatg 360
gggcaatctt caaattacac caagacgcac agtggtttat ttaccctccc cttctcataa 420
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<210> 135
<211> 511
<212> DNA
<213> Homo sapiens
<400> 135
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tgactatgaa cagcttcttg atgtaaagtt agccctggac atggaaatca gtgcttacag 180
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gggttgatgt ggaagaatca gaggcgaagt agtagtgtta gcatctctca ttccgcctca 360
accactggaa atgtttgcat cgaagaaatt gatgttgatg ggaaatttat cccgcttgaa 420
gaacacttct gaacaggatc aaccaatggg aaggcttggg agatgatcag aaaaattgga 480
gacacatcag tcagttataa atatacctca a
<210> 136
<211> 341
<212> DNA
<213> Homo sapiens
<400> 136
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ctgtttcttt tgtctttagc gtaaagctct cctgccatgc agtatctaca taactgacgt 180
gactgccagc aagctcagtc actccgtggt ctttttctct ttccagttct tctctctct 240
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<210> 137
<211> 551
<212> DNA
<213> Homo sapiens
<400> 137
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aattattgtg tcagaagaga ttgaatacct gcttaagaag cttacagaag ctatgggagg 180
aggttggcag caagaacaat ttgaacatta taaaatcaac tttgatgaca gtaaaaatgg 240
cctttctgca tgggaactta ttgagcttat tggaaatgga cagtttagca aaggcatgga 300
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aaagcagggt tacatgatga aaaagggcca cagacggaaa aactggactg aaagatggtt 420
tgtactaaaa cccaacataa tttcttacta tgtgagtgag gatctgaagg ataagaaagg 480
 agacattoto ttggatgaaa attgotgtgt agaagtoott gootgacaaa agatggaaag 540
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 aaatgccttt t
 <210> 138
 <211> 531
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 490
 <223> n = A, T, C or G
 <400> 138
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 ggactgggta gggaaggaaa cttaaaagat caacaaactg ccagcccacg gactgcagag 240
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 acaaagcaca attgagatgg cacttctaga gacagcagct tcaaacccag aaaagggtga 420
 tgagatgaag tttcacatgg ctaaatcagt ggcaaaaaca cagtcttctt tctttctttc 480
 tttcaaggan gcaggaaagc aattaagtgg tcaccttaac ataaggggga c
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<210> 139
<211> 521
<212> DNA
<213> Homo sapiens
<221> misc feature
<222> 517
<223> n = A, T, C or G
<400> 139
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cqqqccttaa aaqatqaaga aaaqatqqaa ctccaggaaa tccaactcaa agaagctaag 360
cacattgcag aagaggcaga taggaagtat gaagaggtgg ctcgtaagtt ggtgatcatt 420
qaaqqaqact tqqaaccqca caqaaqqaac qagcttgagc ttggcaaaag tcccgttgcc 480
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<210> 140
<211> 571
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7
<223> n = A, T, C or G
<400> 140
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taaactctgc tctgagcctc cttgtcgcct gcatttagat ggctcccgca aagaagggtg 180
gcgagaagaa aaagggccgt tctgccatca acgaagtggt aacccgagaa tacaccatca 240
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<210> 141
<211> 531
<212> DNA
<213> Homo sapiens
<400> 141
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cccaagaagc ccaccttctg gtcccaacct gcagacccca cagcagtcag ttggtcaggc 180
cctgctgtag aaggtcactt ggctccattg cctgcttcca accaatgggc aggagaga 240
geetttattt etegeceace catteeteet gtaccageae eteegtttte agteagtgtt 300
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agetgttage ettagagtga ttgeagtgaa caetgtttae acaeegtgaa teeatteeea 420
teagteeatt ceagttggca ceageetgaa ceatttggta cetggtgtta actggagtee 480
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<210> 142
<211> 491
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 410
<223> n = A, T, C or G
<400> 142
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caggaaagtg gaagtgattt gatggagagc agagaagcct atgcacagtg gccgagtcca 480
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cttgtaaagt g
<210> 143
<211> 515
<212> DNA
<213> Homo sapiens
<400> 143
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teaceggeee ateteettee tetttteet aactatgeea ttaaaaetgt tetactggge 240
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qcaqaaqaat cqcttgaacc cgggaggcag aggatgcagt gagccccgat cgcgccactg 480
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<210> 144
<211> 340
 <212> DNA
 <213> Homo sapiens
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cageceaace ceatgageee ecageageat atgeteceaa ateaggeeea gteeceacae 120
ctacaaggec agcagatece taattetete tecaateaag tgegetetee ecageetgte 180
cettetecae ggccaeagte ceagecece cactecagte ettececaag gatgcageet 240
 cagecttete cacaccaegt tteeceacag acaagtteee cacateetgg aetggtagtt 300
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 <210> 145
 <211> 630
 <212> DNA
 <213> Homo sapiens
 <400> 145
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gccacagget gaaggaggg cetgaggcac cgcagcetgc aacceccagg getgcagtec 300
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gacagggcac gggaggtctc agccccactt
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<210> 146
<211> 521
<212> DNA
<213> Homo sapiens
<400> 146
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<211> 562
<212> DNA
<213> Homo sapiens
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ccaggacatc acccagaaac ttttcttcct tcaagtgaag qaaggaatcc ttagcgatga 480
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<211> 820
<212> DNA
<213> Homo sapiens
<400> 148
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gaaaggaaag aacacctgca gaaccggaca gaaattcacc ccggcgatca gctgattgat 180
ctcggtcgac cagaagtcat ggctaaagat gacgaggacg ttgtcaattc cctgggcttt 240
tcgaagtgag tccagcagca gtctgaggta ttcgggccgg ttatgcacct ggaccaccag 300
caccagetee eggggggeee aggtgeeage ettatetaca tteeteaggg tetgateaaa 360
gttcagctgg tacaccaggg accggtaccg cagcgtcagg ttgtccgctc gggctggggg 420
accgccggga ccagggaage cgccgacacg ttggagaccc tgcggatgcc cacagccaca 480
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gaggggtggt ccccaccgcg gccgccggca ccccgcgcg gttcggcgtc cagcaacggt 540 ggggcgaggg cctcgttctt cctttgtcgc ccattgctgc tccagaggac gaagccgcag 600 gcggccacca cgagcgtcag gattagcacc ttccgtttgt agatgcggaa cctcatggtc 660 tccagggccg ggagcgcagc tacagctcga gcgtcggcgc cgccgctagg agccgcggct 720

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eggettegte teegteetet ecatteagea eeaegggtee eggaaaaage teageesegg 780
teccaacege accetagett egttacetge geetegettg
<210> 149
<211> 501
<212> DNA
<213> Homo sapiens
<400> 149
cagattttta tttgcagtcg tcactggggc cgtttcttgc tgcttatttg tctgctagcc 60
tgctcttcca gctgcatggc caggcgcaag gccttgatga catctcgcag ggctgagaaa 120
tgcttggctt gctgggccag agcagattcc gctttgttca caaaggtctc caggtcatag 180
tctggctgct cggtcatctc agagagctca agccagtctg gtccttgctg tatgatctcc 240
ttgagetett ceatageett etectecage teeetgatet gagteatgge ttegttaaag 300
ctggacatct gggaagacag ttcctcctct tccttggata aattgcctgg aatcagcgcc 360
ccqttaqaqc aqqcttccat ctcttctgtt tccatttgaa tcaactgctc tccactgggc 420
ccactgtggg ggctcagctc cttgaccctg ctgcatatct taagggtgtt taaaggatat 480
                                                                   501
tcacaggage ttatgcctgg t
<210> 150
<211> 511
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 457, 479
<223> n = A, T, C or G
<400> 150
ctcctcttqq tacatgaacc caagttgaaa gtggacttaa caaagtatct ggagaaccaa 60
gcattctgct ttgactttgc atttgatgaa acagcttcga atgaagttgt ctacaggttc 120
acagcaaggc cactggtaca gacaatcttt gaaggtggaa aagcaacttg ttttgcatat 180
ggccagacag gaagtggcaa gacacatact atgggcggag acctctctgg gaaagcccag 240
aatgcatcca aagggatcta tgccatggcc ttccgggacg tcttcttctg aagaatcaac 300
cctgctaccg gaagttgggc ctggaagtct atgtgacatt cttcgagatc tacaatggga 360
agetgtttga cetgeteaac aagaaggeea agettgegeg tgetggaaga eggeaagcaa 420
caggtgcaag tggtggggc ttgcaggaac atctggntaa ctctgcttga tgatggcant 480
caaqatqatc gacatgggca gcgcctgcag a
<210> 151
<211> 566
 <212> DNA
 <213> Homo sapiens
 <400> 151
 tcccgaattc aagcgacaaa ttggawagtg aaatggaaga tgcctatcat gaacatcagg 60
 caaatctttt gcgccaagat ctgatgagac gacaggaaga attaagacgc atggaagaac 120
 ttcacaatca agaaatgcag aaacgtaaag aaatgcaatt gaggcaagag gaggaacgac 180
 gtagaagaga ggaagagatg atgattcgtc aacgtgagat ggaagaacaa atgaggcgcc 240
 aaagagagga aagttacagc cgaatgggct acatggatcc acgggaaaga gacatgcgaa 300
 tgggtggcgg aggagcaatg aacatgggag atccctatgg ttcaggaggc cagaaatttc 360
 cacctctagg aggtggtggt ggcataggtt atgaagctaa tcctggcgtt ccaccagcaa 420
 ccatgagtgg ttccatgatg ggaagtgaca tgcgtactga gcgctttggg cagggaggtg 480
```

```
cggggcctgt gggtggacag ggtcctagag gaatggggcc tggaactcca gcaggatatg 540
gtagagggag agaagagtac gaaggc
<210> 152
<211> 518
<212> DNA
<213> Homo sapiens
<400> 152
ttcgtgaaga ccctgactgg taagaccatc actctcgaag tggagcccga gtgacaccat 60
tgagaatgtc aaggcaaaga tccaagacaa ggaaggcatc cctcctgacc agcakaggtt 120
gatetttget gggaaacage tggaagatgg acgeaceetg tetgaetaca acatecagaa 180
agagtecace etgeacetgg tgeteegtet cagaggtggg atgeaaatet tegtgaagae 240
cctgactggt aagaccatca ccctcgaggt ggagcccagt gacaccatcg agaatgtcaa 300
qqcaaaqatc caaqataaqq aaqqcatccc tcctqatcaq cagaggttga tctttgctgg 360
gaaacagctg gaagatggac gcaccctgtc tgactacaac atccagaaag agtccactct 420
gcacttggtc ctgcgcttga gggggggtgt ctaagtttcc ccttttaagg tttcaacaaa 480
tttcattgca ctttcctttc aataaagttg ttgcattc
<210> 153
<211> 542
<212> DNA
<213> Homo sapiens
<400> 153
gcqcqqqtqc gtqqqccact gggtqaccga cttagcctgg ccagactctc agcacctgga 60
agegeeeega gagtgaeage gtgaggetgg gagggaggae ttggettgag ettgttaaac 120
tetgetetga geeteettgt egeetgeatt tagatggete eegeaaagaa gggtggegag 180
aagaaaaagg gccgttctgc catcaacgaa gtggtaaccc gagaatacac catcaacatt 240
cacaagcgca tccatggagt gggcttcaag aagcgtgcac ctcgggcact caaagagatt 300
eggaaatttg ceatgaagga gatgggaact ceagatgtge geattgacae eaggeteaae 360
aaaqctqtct qqqccaaaqq aataaqqaat qtqccatacc gaatccqtqt gcqqctqtcc 420
agaaaacgta atgaggatga agattcacca aataagctat atactttggt tacctatgta 480
cctgttacca ctttcaaaaa tctacagaca gtcaatgtgg atgagaacta atcgctgatc 540
qt
                                                                   542
<210> 154
<211> 411
<212> DNA
<213> Homo sapiens
<400> 154
aattetttat ttaaateaac aaacteatet teeteaagee eeagaceatg gtaggeagee 60
ctccctctcc atcccctcac cccacccctt agccacagtg aagggaatgg aaaatgagaa 120
gccacgaggg cccctgccag ggaaggctgc cccagatgtg tggtgagcac agtcagtgca 180
gctgtggctg gggcagcagc tgccacaggc tcctccctat aaattaagtt cctgcagcca 240
caqctqtqqq aqaaqcatac ttqtaqaaqc aaggccaqtc cagcatcaqa aggcaqaggc 300
agcatcagtg actoccagoo atggaatgaa oggaggacao agagotcaga gacagaacag 360
gccaqgqqqa agaaggagag acagaatagg ccagggcatg gcggtgaggg a
<210> 155
<211> 421
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 173
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```
<223> n = A, T, C or G
<400> 155
tgatgaatct gggtgggctg gcagtagccc gagatgatgg gctcttctct ggggatccca 60
actqqttccc taaqaaatcc aaggagaatc ctcggaactt ctcggataac cagctgcaag 120
agggcaagaa cgtgatcggg ttacagatgg gcaccaaccg cggggcgtct cangcaggca 180
tgactggcta cgggatgcca cgccagatcc tctgatccca ccccaggcct tgcccctgcc 240
ctcccacgaa tggttaatat atatgtagat atatatttta gcagtgacat tcccagagag 300
coccagaget ctcaagetee tttctgtcag ggtgggggt tcaagectgt cctgtcacet 360
ctgaagtqcc tqctqqcatc ctctccccca tqcttactaa tacattccct tccccatagc 420
<210> 156
<211> 670
<212> DNA
<213> Homo sapiens
<400> 156
agcggagete ceteceetgg tggetacaac ceacacacge caggetcagg categageag 60
aactccageg actgggtaac cactgacatt caggtgaagg tgcgggacac ctacctggat 120
acacaggtgg tgggacagac aggtgtcatc cgcagtgtca cgggggggcat gtgctctgtg 180
tacctgaagg acagtgagaa ggttgtcage atttccagtg agcacctgga gcctatcacc 240
bccaccaaga acaacaaggt gaaagtgatc ctgggcgagg atcgggaagc cacgggcgtc 300
ctactgagca ttgatggtga ggatggcatt gtccgtatgg accttgatga gcagctcaag 360
atcctcaacc teegetteet ggggaagete etggaageet gaageaggea gggeeggtgg 420
acttegtegg atgaagagtg atceteette etteeetgge cettggetgt gacacaagat 480
cctcctqcaq qqctaqqcqq attqttctqq atttcctttt qttttcctt ttaggtttcc 540
atcttttccc tccctggtgc tcattggaat ctgagtagag tctgggggag ggtccccacc 600
ttcctgtacc tcctccccac agcttgcttt tgttgtaccg tctttcaata aaaagaagct 660
gtttggtcta
<210> 157
<211> 421
<212> DNA
<213> Homo sapiens
<400> 157
ggttcacage actgctgctt gtgtgttgcc ggccaggaat tecaggctca caaggctatc 60
ttagcagctc gttctccggt ttttagtgcc atgtttgaac atgaaatgga ggagagcaaa 120
aagaatcgag ttgaaatcaa tgatgtggag cctgaagttt ttaaggaaat gatgtgcttc 180
atttacacgg ggaaggctcc aaacctcgac aaaatggctg atgatttgct ggcagctgct 240
gacaagtatg ccctggagcg cttaaaggtc atgtgtgagg atgccctctg cagtaacctg 300
teegtggaga acgetgeaga aatteteate etggeegace teeacagtge agateagttg 360
aaaactcagg cagtggattt catcaactat catgcttcgg atgtcttgga gacctcttgg 420
<210> 158
<211> 321
<212> DNA
<213> Homo sapiens
<400> 158
tegtagecat ttttetgett etttggagaa tgaegecaca etgaetgete attgtegttg 60
gttccatgcc aattggtgaa atagaacctc atccggtagt ggagccggag ggacatcttg 120
tcatcaacgg tgatggtgcg atttggagca taccagagct tggtgttctc gccatacagg 180
qcaaaqaqqt tqtqacaaaq aggagaqata cqqcatqcct qtgcaqccct gatgcacagt 240
tectetgetg tgtactetec actgeccage eggagggget ecetgteega cagatagaag 300
                                                                   321
atcacttcca cccctggctt g
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49

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<210> 159
<211> 596
<212> DNA
<213> Homo sapiens
<400> 159
tggcacactg ctcttaagaa actatgawga tctgagattt ttttgtgtat gtttttgact 60
cttttgagtg gtaatcatat gtgtctttat agatgtacat acctccttgc acaaatggag 120
gggaattcat tttcatcact gggagtgtcc ttagtgtata aaaaccatgc tggtatatgg 180
cttcaagttg taaaaatgaa agtgacttta aaagaaaata ggggatggtc caggatctcc 240
actgataaga ctgtttttaa gtaacttaag gacctttggg tctacaagta tatgtgaaaa 300
aaatgaqact tactgggtga ggaaattcat tqtttaaaga tggtcgtgtg tgtgtgtgtg 360
ttgaaattac tgkgtaaata tatgtytgat aatgatttgc tytttgvcma ctaaaattag 480
gvctgtataa gtwctaratg cmtccctggg kgttgatytt ccmagatatt gatgatamcc 540
cttaaaattg taaccygcct ttttcccttt gctytcmatt aaagtctatt cmaaag
<210> 160
<211> 515
<212> DNA
<213> Homo sapiens
<400> 160
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cagigtcaga ggcccgcgtt cagcccaaga atgtggattt tctctcccta ttgatcacag 120
tgggtgggtt tcttcagaaa agccccagag gcagggacca gtgagctcca aggttagaag 180
tggaactgga aggetteagt cacatgetge ttecaegett ceaggetggg cageaaggag 240
gagatgecca tgaegtgeca ggtetececa tetgaeacea gtgaagtetg gtaggaeage 300
agcegeacge etgeetetge caggaggeea ateatggtag geageattge agggteagag 360
gtctgagtcc ggaataggag caggggcagg tccctgcgga gaggcacttc tggcctgaag 420
acageteeat tgageeeetg cagtacaggy gtagtgeett ggaceaagee cacageetgg 480
                                                                 515
taaggggcgc ctgccagggc cacggccagg aggca
<210> 161
<211> 936
<212> DNA
<213> Homo sapiens
<400> 161
taatttetta gtegtttgga ateettaage atgeaaaage tttgaacaga agggtteaca 60
aaggaaccag ggttgtctta tggcatccag ttaagccaga gctgggaatg cctctgggtc 120
atecacatea qqaqcaqaaq caettqaett qteggteetq etqeeacgqt ttgggegeec 180
accaegocea egtecacete gtecteceet geogocaegt eetgggegge caaggtetee 240
aaaattgatc teeagetgag aegttatate atttgetgge tteeggaaat gatggteeat 300
aaccgaatct tcagcatgag cctcttcact ctttgattta tgaagaacaa atcccttctt 360
ccactgccca tcagcacctt catttggttt tcggatatta aattctactt ttgcccggtc 420
cttattttga atagcettee aeteateeaa agteatetet tttggaceet cetettttac 480
ctcttcaact tcattctcct tattttcagt qtctgccact ggatgatgtt cttcaccttc 540
aggtgtttcc tcagtcacat ttgattgatc caagtcagtt aattcgtctt tgacagttcc 600
ccagttgtga gatccgctac ctccacgttt gtcctcgtgc ttcaggccag atctatcact 660
tccactatgc ctatcaaatt cacgtttgcc acgagaatca aatccatctc ctcggcccat 720
tocacqtoca cqqcccctc qacctottcc aagaccacca cqacctcgaa tagqtcgqtc 780
aataatcggt ctatcaactg aaaattcgcc tccttcaccc ttttcttcaa gtggcttttc 840
quatetteqt teacquagtq qteqeettte tqqtetteta teaattattt teeetteace 900
ctgaagttgt tgatcaggtc ttcttccaac tcgtgc
                                                                 936
```

<210> 162

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<211> 950
<212> DNA
<213> Homo sapiens
<400> 162
aagcggatgg acctgagtca gccgaatcct. agccccttcc cttgggcctg ctgtggtgct 60
cgacatcagt gacagacgga agcagcagac catcaaggct acgggaggcc cgggggcgctt 120
gcgaagatga agtttggctg cctctccttc cggcagcctt atgctggctt tgtcttaaat 180
ggaatcaaga ctgtggagac gcgctggcgt cctctgctga gcagccagcg gaactgtacc 240
ategeegtee acattgetea cagggactgg gaaggegatg cetgteggga getgetggtg 300
gagagactcg ggatgactcc tgctcagatt caggccttgc tcaggaaagg ggaaaagttt 360
ggtcgaggag tgatagcggg actcgttgac attggggaaa ctttgcaatg ccccgaagac 420
ttaactcccg atgaggttgt ggaactagaa aatcaagctg cactgaccaa cctgaagcag 480
aagtacctga ctgtgatttc aaaccccagg tggttactgg agcccatacc taggaaagga 540
ggcaaggatg tattccaggt agacatccca gagcacctga tccctttggg gcatgaagtg 600
tgacaagtgt gggctcctga aaggaatgtt ccrgagaaac cagctaaatc atggcacctt 660
caatttgcca tcgtgacgca gacctgtata aattaggtta aagatgaatt tccactgctt 720
tggagagtcc cacccactaa gcactgtgca tgtaaacagg ttcctttgct cagatgaagg 780
aagtaggggg tggggctttc cttgtgtgat gcctccttag gcacacaggc aatgtctcaa 840
gtactttgac cttagggtag aaggcaaagc tgccagtaaa tgtctcagca ttgctgctaa 900
ttttggtcct gctagtttct ggattgtaca aataaatgtg ttgtagatga
<210> 163
<211> 475
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 301, 317, 331, 458, 464, 470
<223> n = A, T, C or G
<400> 163
tcgagcggcc gcccgggcag gtgtcggagt ccagcacggg aggcgtggtc ttgtagttgt 60
tctccggctg cccattgctc tcccactcca cggcgatgtc gctgggatag aagcctttga 120
ccaqqcaqqt caqqctqacc tggttcttgg tcatctcctc ccgggatggg ggcagggtgt 180
acacctgtgg ttctcggggc tgccctttgg ctttggagat ggttttctcg atgggggctg 240
ggagggettt gttggagace ttgcacttgt actcettgce attcaaccag teetggtgca 300
ngacggtgag gacgctnacc acacggtacg ngctggtgta ctgctcctcc cgcggctttg 360
tcttggcatt atgcacctcc acgccgtcca cgtaccaatt gaacttgacc tcagggtctt 420
 cgtggctcac gtccaccacc acgcatgtaa cctcaaanct cggncgcgan cacgc
 <210> 164
 <211> 476
 <212> DNA
 <213> Homo sapiens
 <400> 164
 agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60
 ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
 gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctgca 180
 ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240
 ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac aggtgtacac 300
 cctgccccca tcccgggagg agatgaccaa gaaccaggtc agcctgacct gcctggtcaa 360
 aggettetat eccagegaca tegecegtgg agtgggagag caatgggeag eeggagaaca 420
 actacaagac cacgcctccc gtgctggact ccgacacctg ccgggcggcc gctcga
```

```
<211> 256
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 10, \overline{3}7, 249
<223> n = A, T, C or G
<400> 165
agegtggttn eggeegaggt ceeaaceaag getgeancet ggatgeeate aaagtettet 60
qcaacatqqa qactqqtqaq acctqcqtqt accccactca qcccaqtqtq qcccaqaaqa 120
actggtacat cagcaagaac cccaaggaca agaggcatqt ctggttcggc gagagcatga 180
ccgatggatt ccagttcgag tatggcggcc agggctccga ccctgccgat gtggacctgc 240
ccgggcggnc gctcga
<210> 166
<211> 332
<212> DNA
<213> Homo sapiens
<400> 166
agegtggteg eggeegaggt caagaacccc geeggacct geegtgacct caagatgtgc 60
cactctgact ggaagagtgg agagtactgg attgacccca accaaggctg caacctggat 120
gccatcaaag tcttctgcaa catggagact ggtgagacet gcgtgtaccc cactcagecc 180
agtgtggccc agaagaactg gtacatcagc aagaacccca aggacaagag gcatgtctgg 240
ttcggcgaga gcatgaccga tggattccag ttcgagtatg gcggccaggg ctccgaccct 300
geegatgtgg acetgeeegg geggeegete ga
                                                                    332
<210> 167
<211> 332
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 77, 109, 136, 184, 198
<223> n = A, T, C or G
<400> 167
tegageggte geeegggeag gtecacateg geagggtegg agecetggee geeatacteg 60
aactggaatc catcggncat gctctcgccg aaccagacat gcctcttgnc cttggggttc 120
ttgctgatgt accagntctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccantctcca tgttgcanaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact ctccactctt ccagacagag tggcacatct tgaggtcacg gcaggtgcgg 300
geggggttet tgaceteggt egegaceaeg et
<210> 168
<211> 276
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 72, 84
<223> n = A, T, C or G
<400> 168
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```
tegageggee geeegggeag gteeteetea gageggtage tgttettatt geeeeggeag 60
cctccataga tnaagttatt gcangagttc ctctccacgt caaagtacca gcgtgggaag 120
gatgcacggc aaggcccagt gactgcgttg gcggtgcagt attcttcata gttgaacata 180
tcgctggagt ggacttcaga atcctgcctt ctgggagcac ttgggacaga ggaatccgct 240
gcattcctgc tggtggacct cggccgcgac cacgct
<210> 169
<211> 276
<212> DNA
<213> Homo sapiens
<400> 169
agegtggteg eggeegaggt ceaceageag gaatgeageg gatteetetg teecaagtge 60
tcccagaagg caggattctg aagaccactc cagcgatatg ttcaactatg aagaatactg 120
caccgccaac gcagtcactg ggccttgccg tgcatccttc ccacgctggt actttgacgt 180
ggagaggaac teetgeaata aetteateta tggaggetge eggggeaata agaacageta 240
ccgctctgag gaggacctgc ccgggcggcc gctcga
<210> 170
<211> 332
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 294
<223> n = A, T, C \text{ or } G
<400> 170
tegageggee geeegggeag gtecacateg geagggtegg ageeetggee geeatacteg 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccaqtact ctccactctt ccagccagaa tggcacatct tgaggtcacg gcangtgcgg 300
geggggttet tgacetegge egegaceaeg et
<210> 171
<211> 333
<212> DNA
<213> Homo sapiens
<400> 171
agegtggteg eggeegaggt caagaaacce egeeegeace tgeegtgace teaagatgtg 60
ccactetggc tggaagagtg gagagtactg gattgacccc aaccaagget gcaacetgga 120
tgccatcaaa gtcttctgca acatggagac tggtgagacc tgcgtgtacc ccactcagcc 180
 cagtgtggcc cagaagaact ggtacatcag caagaacccc aaggacaaga ggcatgtctg 240
 gctcggcgag agcatgaccg atggattcca gttcgagtat ggcggccagg gctccgaccc 300
 tgccgatgtg gacctgcccg ggcggccgct cga
                                                                    333
 <210> 172
 <211> 527
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 46, 125, 140, 148, 220, 229, 291, 388, 456
 <223> n = A,T,C or G
```

```
<400> 172
agegtggteg eggeegaggt cetgteagag tggeaetggt agaagnteea ggaaceetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctgnaatgg ggcccatgan atggttgnct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgn gggcggtgng gtccgcctaa 240
aaccatgtte etcaaagate atttgttgee caacactggg ttgetgacca naagtgeeag 300
gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctgntc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgctgtct ttttccttcc aatcangggc tcgctcttct gaatattctt 480
cagggcaatg acataaattg tatattcggt tcccggttcc aggccag
<210> 173
<211> 635
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 444, 453, 517, 540, 546, 551, 573, 593
<223> n = A, T, C or G
<400> 173
tcgagcggcc gcccgggcag gtccaccaca cccaattcct tgctggtatc atggcagccg 60
ccacqtqcca ggattaccqq ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
quaqtqqtcc ctcqqcccq ccctqqtqtc acaqaqqcta ctattactqq cctqqaaccq 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteacceae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatett tgangaacat ggntttagge ggaccacace ggccacaacg 480
qqcacccca taaqqcataq qccaaqaaca tacccqncga atqtaggaca agaaqctctn 540
teteanacaa neateteatg ggeceeatte cangacaett etgagtaeat cantteatgg 600
catcctggtg gcactgataa aaacccttac agtta
<210> 174
<211> 572
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 457, 511, 520, 552, 568
<223> n = A, T, C or G
<400> 174
agcgtggtcg cgggcgaggt cctgtcagag tggcactggt agaagttcca ggaaccctga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca gaagtgccag 300
gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgtctgtc tttttccttc caatcanggg ctcgctcttc tgattattct 480
tcagggcaat gacataaatt gtatattcgg ntcccgggtn cagccaataa taataaccct 540
ctgtgacacc anggcggggc cgaagganca ct
```

```
<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 247
<223> n = A, T, C or G
<400> 175
agcgtggtcg cggccgaggt cctcaccaga ggtaccacct acaacatcat agtggaggca 60
ctgaaagacc agcagaggca taaggttcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaaggct tgaaccaacc tacggatgac tcgtgctttg acccctacac agtttcccat 180
tatgccqttq gagatgagtq ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttangct ttggaagtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
ggtgtgaact acaagattgg agagaagtgg gaccgtcagg gagaaaatgg acctgcccgg 360
geggeegete ga
<210> 176
<211> 372
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 251
<223> n = A, T, C or G
<400> 176
tegageggee geeegggeag gtecatttte teeetgaegg teeeacttet etecaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
 caageetteg ntgacagagt tgeccaeggt aacaacetet teeegaacet tatgeetetg 300
 ctggtctttc agtgcctcca ctatgatgtt gtaggtggta cctctggtga ggacctcggc 360
 cgcgaccacg ct
 <210> 177
 <211> 269
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 94, \overline{2}25
 <223> n = A, T, C or G
 <400> 177
 agcgtggccg cggccgaggt ccattggctg gaacggcatc aacttggaag ccagtgatcg 60
 tctcagcctt ggttctccag ctaatggtga tggnggtctc agtagcatct gtcacacgag 120
 cccttcttgg tgggctgaca ttctccagag tggtgacaac accctgaget ggtctgcttg 180
 tcaaagtgtc cttaagagca tagacactca cttcatattt ggcgnccacc ataagtcctg 240
 atacaaccac ggaatgacct gtcaggaac
 <210> 178
 <211> 529
 <212> DNA
 <213> Homo sapiens
```

```
<400> 178
tcgagcggcc gcccgggcag gtcctcagac cgggttctga gtacacagtc agtgtggttg 60
ccttgcacga tgatatggag agccagccc tgattggaac ccagtccaca gctattcctg 120
caccaactga cctgaagttc actcaggtca caccaacaag cctgagcgcc cagtggacac 180
cacccaatgt tcagctcact ggatatcgag tgcgggtgac ccccaaggag aagaccggac 240
caatgaaaga aatcaacctt geteetgaca geteateegt ggttgtatea ggaettatgg 300
cggccaccaa atatgaagtg agtgtctatg ctcttaagga cactttgaca agcagaccag 360
ctcaggqtgt tgtcaccact ctggagaatg tcagcccacc aagaagggct cgtgtgacag 420
atgctactga gaccaccatc accattagct ggagaaccaa gactgagacg atcactggct 480
tecaagttga tgccgttcca gccaatggac ctcggccgcg accacgctt
<210> 179
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 64
<223> n = A, T, C or G
<400> 179
agcgtggtcg cggccgaggt ctggccgaac tgccagtgta cagggaagat gtacatgtta 60
tagntettet egaagteeeg ggeeageage teeaeggggt ggteteetge eteeaggege 120
ttctcattct catggatctt cttcacccgc agcttctgct tctcagtcag aaggttgttg 180
tecteatece teteatacag ggtgaccagg aegttettga gecagteceg catgegeagg 240
gggaattcgg tcagctcaga gtccaggcaa ggggggatgt atttgcaagg cccgatgtag 300
tecaagtgga gettgtggee ettettggtg ceetecaagg tgeaetttgt ggeaaagaag 360
tggcaggaag agtcgaaggt cttgttgtca ttgctgcaca ccttctcaaa ctcgccaatg 420
ggggctgggc agacctgccc gggcggccgc tcga
<210> 180
<211> 454
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 55, 299, 317, 332, 342, 348
<223> n = A, T, C or G
<400> 180
tcgagcggcc gcccgggcag gtctgcccag ccccattgg cgagtttgag aaggngtgca 60
gcaatgacaa caagacette gactetteet gccacttett tgccacaaag tgcaccetgg 120
agggcaccaa gaagggccac aagctccacc tggactacat cgggccttgc aaatacatcc 180
ccccttgcct ggactctgag ctgaccgaat tccccctgcg catgcgggac tggctcaaga 240
acgtcctggt caccctgtat gagagggatg aggacaacaa ccttctgact gagaagcana 300
agctgcgggt gaagaanatc catgagaatg anaagcgcct gnaggcanga gaccaccccg 360
tggagctgct ggcccgggac ttcgagaaga actataacat gtacatcttc cctgtacact 420
ggcagttcgg ccagacctcg gccgcgacca cgct
<210> 181
<211> 102
<212> DNA
<213> Homo sapiens
<220>
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```
<221> misc feature
<222> 8, 47, 60, 67
<223> n = A,T,C or G
<400> 181
agcgtggntg cggacgacgc ccacaaagcc attgtatgta gttttanttc agctgcaaan 60
aataceneca quatecacet tactaaceag catatgeaga ca
<210> 182
<211> 337
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 169, 195, 253, 314
<223> n = A, T, C or G
<400> 182
tcgagcggtc gcccgggcag gtctgggcgg atagcaccgg gcatattttg gaatggatga 60
ggtctggcac cctgagcagc ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggtt ctgagtctgt gggatagctg ccatgaagna acctgaagga 180
ggcgctggct ggtangggtt gattacaggg ctgggaacag ctcgtacact tgccattctc 240
tgcatatact ggntagtgag gcgagcctgg cgctcttctt tgcgctgagc taaagctaca 300
tacaatggct ttgnggacct cggccgcgac cacgctt
<210> 183
<211> 374
<212> DNA
<213> Homo sapiens
<400> 183
tcgagcggcc gcccgggcag gtccattttc tccctgacgg tcccacttct ctccaatctt 60
gtagttcaca ccattgtcat gacaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagaag ttgeecacgg taacaacete tteecgaace ttatgeetet 300
gctggtcttt caagtgcctc cactatgatg ttgtaggtgg cacctctggt gaggacctcg 360
 gccgcgacca cgct
 <210> 184
 <211> 375
 <212> DNA ·
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> 30, 174, 248, 285, 306, 332, 345, 368
 <223> n = A, T, C or G
 <400> 184
 agegtggttt geggeegagg teeteacean aggtgeeace tacaacatea tagtggagge 60
 actgaaagac cagcagaggc ataaggttcg ggaagaggtt gttaccgtgg gcaactctgt 120
 caacgaaggc ttgaaccaac ctacggatga ctcgtgcttt gacccctaca cagnttccca 180
 ttatgccgtt ggagatgagt gggaacgaat gtctgaatca ggctttaaac tgttgtgcca 240
 gtgcttangc tttggaagtg gtcatttcag atgtgattca tctanatggt gtcatgacaa 300
 tggtgngaac tacaagattg gagagaagtg gnaccgtcag ggganaaaat ggacctgccc 360
 gggcggcncg ctcga
```

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<210> 185
<211> 148
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature <222> 28, 36, 86
<223> n = A, T, C or G
<400> 185
agcgtggtcg cggccgaggt ctggcttnct gctcangtga ttatcctgaa ccatccaggc 60
caaataagcg ccggctatgc ccctgnattg gattgccaca cggctcacat tgcatgcaag 120
tttgctgagc tgaaggaaaa gattgatc
                                                                    148
<210> 186
<211> 397
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 78
<223> n = A, T, C or G
<400> 186
tegageggee geeegggeag gteeaattga aacaaacagt tetgagaceg ttettecace 60
actgattaag agtggggngg cgggtattag ggataatatt catttagcct tctgagcttt 120
etgggcagae ttggtgaeet tgccagetee agcageette tggtecaetg etttgatgae 180
acceacegea actgtetgte teatateaeg aacageaaag egaceeaaag gtggatagte 240
tqaqaaqete tcaacacaca tqqqettqee aqqaaccata tcaacaatqq qeaqeatcac 300
cagacticaa gaatttaagg gccatcttcc agctttttac cagaacggcg atcaatcttt 360
teetteaget cageaaaett geatgeaatg tgageeg
<210> 187
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 145, 286, 363, 365, 425, 433, 452, 462, 471, 512, 514, 534,
536, 540, 565, 583
<223> n = A, T, C \text{ or } G
<400> 187
tegageggee geeegggeag gteeagaggg etgtgetgaa gtttgetget geeactggag 60
ccactccaat tgctggccgc ttcactcctg gaaccttcac taaccagatc caggcagect 120
teegggagee aeggettett gtggntaetg aeeceaggge tgaceaceag eeteteaegg 180
aggeatetta tgttaaceta cetaceattg egetgtgtaa cacagattet eetetgeget 240
atgtggacat tgccatccca tgcaacaaca agggagctca ctcagngggg tttgatgtgg 300
tggatgctgg ctcgggaagt tctgcgcatg cgtggcacca tttcccgtga acacccatgg 360
qangncatgc ctgatctgga cttctacaga gatcctgaag agattgaaaa agaagaacag 420
qctgnttgct ganaaagcaa gtgaccaagg angaaatttc angggtgaaa nggactgctc 480
ccgctcctga attcactgct actcaacctg angntgcaga ctggtcttga aggngnacan 540
gggccctctg ggcctattta agcancttcg gtcgcgaaca cgnt
```

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<210> 188
<211> 579
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7, 136, 486
<223> n = A, T, C \text{ or } G
<400> 188
agcgtgngtc gcggccgagg tgctgaatag gcacagaggg cacctgtaca ccttcagacc 60
agtetgeaac etcaggetga gtageagtga acteaggage gggageagte catteaccet 120
gaaattcctc cttggncact gccttctcag cagcagcctg ctcttcttt tcaatctctt 180
caggatetet gtagaagtac agateaggea tgaceteeca tgggtgttea egggaaatgg 240
tgccacgcat gcgcagaact tcccgagcca gcatccacca catcaaaccc actgagtgag 300
ctcccttgtt gttgcatggg atgggcaatg tccacatagc gcagaggaga atctgtgtta 360
cacagegeaa tggtaggtag gttaacataa gatgeeteeg egagaagetg gtggteagee 420
ctggggtcaa gtaaccacaa gaagccgtgg ctcccggaag gctgcctgga tctggttagt 480
gaaggntcca ggagtgaagc ggccaacaat tggagtggct tcagtggcaa gcagcaaact 540
teageacaag ecetetggae etgeeeggeg geegetega
<210> 189
<211> 374
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 41, \overline{2}80, 314, 330, 350, 353
<223> n = A, T, C or G
<400> 189
tegageggee geeegggeag gtecatttte teeetgaegg neceaettet etceaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat qaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgeccaeggt aacaaceten teecegaace ttatgeetet 300
gctgggcttt cagngcctcc actatgatgn tgtagggggg cacctctggn gangacctcg 360
gccgcgacca cgct
<210> 190
<211> 373
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 247, 304, 306, 332, 337
<223> n = A, T, C or G
<400> 190
agcgtggtcg cggccgaggt cctcaccaga ggtgccacct acaacatcat agtggaggca 60
ctgaaagacc agcagaggca taaggctcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaagget tgaaccaacc tacggatgac tegtgetttg acccetacac agttteccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttangct ttggaagtgg gtcatttcag atgtgattca tctagatggt gccatgacaa 300
tggngngaac tacaagattg gagagaagtg gnaccgncag ggagaaaatg gacctgcccg 360
```

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373
ggcggccgct cga
<210> 191
<211> 354
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 218, 299, 306, 326, 333, 337, 341
<223> n = A, T, C or G
<400> 191
agcgtggtcg cggccgaggt ccacatcggc agggtcggag ccctggccgc catactcgaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
getgatgtac cagttettet gggccacact gggctgagtg gggtacacgc aggteteacc 180
agtotocatg ttgcagaaga ctttgatggc atccaggntg caaccttggt tggggtcaat 240
ccaqtactct ccactettee agecaqagtg gcacatettg aggteacgge aggtgcggne 300
gggggntttt gcggctgccc tctggncttc ggntgtnctc natctgctgg ctca
<210> 192
<211> 587
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 276
<223> n = A,T,C or G
<400> 192
tegageggee geeegggeag gtetegeggt egeaetggtg atgetggtee tgttggteee 60
congecte ctggacetec tggccccct ggtcctcca gegetggttt cgacttcage 120
ttcctgcccc agccacctca agagaagget cacgatggtg gccgctacta ccgggctgat 180
gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagcctgagc 240
cagcagateg agaacateeg gageecagag ggeagnegea agaaceeege eegeacetge 300
cgtgacctca agatgtgcca ctctgactgg aagagtggag agtactggat tgaccccaac 360
caagetgeaa cetggatgee atcaaagtet tetgeaacat ggagactggt gagacetgeg 420
tgtaccccac tcagcccagt gtggcccaaa agaactggta catcagcaag aaccccaagg 480
acaagaagca tgtctggttc ggcgagaaca tgaccgatgg attccagttc gagtatggcg 540
ggcagggetc cgaccctgcc gatggggacc ttggccgcga acacgct
                                                                   587
<210> 193
<211> 98
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9, 33, 58, 71, 90
<223> n = A,T,C or G
<400> 193
agcgtggnng cggccgaggt ataaatatec agnecatate etecetecae acgetganag 60
atgaagctgt ncaaagatct cagggtggan aaaaccat
<210> 194
<211> 240
```

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<212> DNA
<213> Homo sapiens
<400> 194
tcgagcggcc gcccgggcag gtccttcaga cttggactgt gtcacactgc caggcttcca 60
gggctccaac ttgcagacgg cctgttgtgg gacagtctct gtaatcgcga aagcaaccat 120
ggaagacctg ggggaaaaca ccatggtttt atccaccctg agatctttga acaacttcat 180
ctctcagcgt gcggagggag gctctggact ggatatttct acctcggccg cgaccacgct 240
<210> 195
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 22, \overline{3}7, 39, 105, 268, 276, 302, 323, 331, 335, 347, 351,
<223> n = A, T, C or G
<400> 195
cgagcggcg accgggcagg tncagactcc aatccanana accatcaagc cagatgtcag 60
aagctacacc atcacaggtt tacaaccagg cactgactac aaganctacc tgcacacctt 120
qaatqacaat qctcqqaqct cccctqtqqt catcqacqcc tccactqcca ttqatqcacc 180
atecaacetg cqttteetgg ccaccacace caatteettg etggtateat ggeageegee 240
acgtgccagg attaccggta catcatenag tatganaagc ctgggcctcc tcccagagaa 300
gnggtccctc ggccccgccc tgntgtccca naggntacta ttactgngcc ngcaaccggc 360
aaccgatatc nattttgnca ttggccttca acaataatta
<210> 196
<211> 494
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 19, 83, 168, 252, 271, 292, 430
<223> n = A, T, C or G
<400> 196
agegtggttc geggeegang teetgteaga gtggeactgg tagaagttee aggaaccetg 60
aactgtaagg gttcttcatc agngccaaca ggatgacatg aaatgatgta ctcagaagtg 120
tectggaatg gggeceatga gatggttgte tgagagagag ettettgnee tgtettttte 180
cttccaatca ggggctcgct cttctgatta ttcttcaggg caatgacata aattgtatat 240
tegggteeeg gnteeaggee agtaatagta neetetgtga caccagggeg gngeegaggg 300
accacttctc tgggaggaga cccaggcttc tcatacttga tgatgtaacc ggtaatcctg 360
gcacgtggcg gctgccatga taccagcaag gaattggggt gtggtggcca ggaaacgcag 420
gttggatggn gcatcaatgg cagtggaggc cgtcgatgac cacaggggga gctccgacat 480
tgtcattcaa ggtg
<210> 197
<211> 118
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
```

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<222> 8, 71, 96
<223> n = A, T, C or G
<400> 197
agegtggneg eggeegaggt geagegeggg etgtgeeace ttetgetete tgeecaacga 60
taaggagggt neetgeeece aggagaacat taactnteee cageteggee tetgeegg
<210> 198
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 41, 53, 98, 195, 350
<223> n = A, T, C or G
<400> 198
tegageggee geeegggeag gttttttttg etgaaagtgg ntactttatt ggntgggaaa 60
gggagaaget gtggtcagec caagagggaa tacagagnee cgaaaaaggg gagggcaggt 120
gggctggaac cagacgcagg gccaggcaga aactttetet ceteaetget cagectggtg 180
gtggctggag ctcanaaatt gggagtgaca caggacacct tcccacagcc attgcggcgg 240
catttcatct ggccaggaca ctggctgtcc acctggcact ggtcccgaca gaagcccgag 300
ctggggaaag ttaatgttca cctgggggca ggaaccctcc ttatcattgn gcagagagca 360
gaaggtggca cagcccgcgc tgcacctcgg ccgcgaccac qct
<210> 199
<211> 167
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 92, 107
<223> n = A, T, C or G
<400> 199
tcgagcggcc gcccgggcag gtccaccata agtcctgata caaccacgga tgagctgtca 60
ggagcaaggt tgatttettt cattggteeg gnetteteet tgggggneae eegeaetega 120
tatccagtga getgaacatt gggtggcgtc cactgggcgc tcaggct
<210> 200
<211> 252
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 210, 226, 227, 230, 236
<223> n = A, T, C \text{ or } G
<400> 200
tegageggtt egeeegggea ggtecaceac acceaattee ttgetggtat catggeagee 60
gccacgtgcc aggattaccg gctacatcat caagtatgag aagcctgggt ctcctcccag 120
agaageggte eeteggeece geeetggtgt cacagagget actattactg geetggaace 180
gggaaccgaa tatacaattt atgtcattgn cctgaagaat aatcannaan agcgancccc 240
tgattggaag ga
```

```
<210> 201
<211> 91
<212> DNA
<213> Homo sapiens
<400> 201
ttttttttt tttttttt tttttt t
<210> 202
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 9, 354
<223> n = A, T, C or G
<400> 202
tegageggne geeegggeag gtetgeeaac accaagattg geeeeegeeg catecacaca 60
gtccgtgtgc ggggaggtaa caagaaatac cgtgccctga ggttggacgt ggggaatttc 120
tectgggget cagagtgttg tactegtaaa acaaggatea tegatgttgt etacaatgea 180
tetaataaeg agetggtteg taccaagaee etggtgaaga attgeategt geteategae 240
agcacaccgt accgacagtg gtacgagtcc cactatgcgc tgcccctggg ccgcaagaag 300
ggagccaagc tgactcctga ggaagaagag attttaaaca aaaaacgatc taanaaaaaa 360
aaaacaat
<210> 203
<211> 340
<212> DNA
<213> Homo sapiens
<400> 203
agcgtggtcg cggccgaggt gaaatggtat tcagcttcct ggcacttctg gtcagcaacc 60
cagtgttggg caacaaatga tctttgagga acatggtttt aggcggacca caccgcccac 120
aacggccacc cccataaggc ataggccaag accatacccg ccgaatgtag gacaagaagc 180
teteteteag acaaceatet catgggeece attecaggae acttetgagt acateattte 240
atgtcatcct gttggcactg atgaagaacc cttacagttc agggttcctg gaacttctac 300
cagtgccact ctgacaggac ctgcccgggc ggccgctcga
<210> 204
<211> 341
<212> DNA
<213> Homo sapiens
<400> 204
tegageggee geeegggeag gteetgteag agtggeaetg gtagaagtte eaggaaceet 60
gaactgtaag ggttcttcat cagtgccaac aggatgacat gaaatgatgt actcagaagt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcgg 180
egggtatggt ettggeetat geettatggg ggtggeegtt gtgggeggtg tggteegeet 240
aaaaccatgt tootcaaaga toatttgttg cocaacactg ggttgctgac cagaagtgcc 300
aggaagctga ataccatttc acctcggccg cgaccacgct a
<210> 205
<211> 770
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> 529, 591, 623, 626, 629, 630, 656, 702, 709, 712, 717, 743,
746, 749, 759, 762, 766
<223> n = A,T,C or G
<400> 205
tegagegee geeegggeag gteteeette ttgeggeeea ggggeagege atagtgggae 60
togtaccact gtoggtacgg tgtgctgtog atgagcacga tgcaattott caccagggtc 120
ttggtacgaa ccagctcgtt attagatgca ttgtagacaa catcgatgat ccttgtttta 180
cgagtacaac actctgagcc ccaggagaaa ttccccacgt ccaacctcag ggcacggtat 240
ttettgttac etcecegeac aeggactgtg tggatgegge gggggecaag etgacteetg 300
aggaagaaga gattttaaac aaaaaacgat ctaaaaaaaat tcagaagaaa tatgatgaaa 360
ggaaaaagaa tgccaaaatc agcagtctcc tggaggagca gttccagcag ggcaagcttc 420
ttgcqtqcat cqcttcaagg ccqggacagt gtgaccgagc agatggctat gtgctaqagg 480
qcaaaqaaqt qqaqttctat cttaaqaaaa tcaqqqccca qaatqqtqnq tcttcaacta 540
atccaaaggg gagtttcaga ccagtgcaat cagcaaaaac attgatactg ntggccaaat 600
ttattggtgc agggcttgca cantangann ggctgggtct tggggcttgg attggnacaa 660
getttggcag cettttettt ggttttgcca aaaacetttt gntgaagang anacetnggg 720
cggacccctt aaccgattcc acnccnggng gcgttctang gncccncttg
<210> 206
<211> 810
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 574, 621, 625, 636, 668, 673, 704, 728, 743, 767, 772, 786,
789, 807, 809, 810
<223> n = A,T,C or G
<400> 206
agegtggteg eggeegaggt etgetgette agegaagggt ttetggeata accaatgata 60
aggetgecaa agaetgttee aataceagea eeagaaceag eeacteetae tgttgeagea 120
cctgcaccaa taaatttggc agcagtatca atgtctctgc tgattgcact ggtctgaaac 180
tccctttqqa ttaqctqaqa cacaccattc tqqqccctqa ttttcctaaq ataqaactcc 240
aactetttge cetetageae atageeatet geteggteae aetgteeegg eettgaageg 300
atgcacqcaa gaagcttgcc ctgctggaac tgctcctcca ggagactgct gattttggca 360
ttcttttcc tttcatcata tttcttctga atttttttag atcgttttt gtttaaaatc 420
tettetteet caggagteag ettggeecee geegeateea cacagteegt gtgeggggag 480
gtaacaagaa ataccgtgcc ctgaggttgg acgtggggaa tttctcctgg ggctcagagt 540
ggtqtactcg taaaacaagg atcatcgatg gtgnctacaa tgcatctaat aacgagctgg 600
gtcggaccca aagaacctgg ngaanaaatg gatcgnctca tcgacaggac accgtacccg 660
acaggggnac ganteceact atgegettge ecetgggeeg caanaaagga aaactgeeeg 720
ggeggeente gaaageecaa ttntggaaaa aateeateae aetgggngge engtegagea 780
tgcatntana ggggcccatt ccccctnann
<210> 207
<211> 257
<212> DNA
<213> Homo sapiens
<400> 207
togagoggco gocogggcag gtococaaco aaggotgcaa cotggatgco atcaaagtot 60
tetgeaacat ggagaetggt gagaeetgeg tgtaceecac teageecagt gtggeecaga 120
agaactggta catcagcaag aaccccaagg acaagaggca tgtctggttc ggcgagagca 180
```

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tgaccgatgg attccagttc gagtatggcg gccagggctc cgaccctgcc gatgtggacc 240
teggeegega ceaeget
<210> 208
<211> 257
<212> DNA
<213> Homo sapiens
<400> 208
agegtggteg eggeegaggt ceacategge agggteggag eeetggeege catactegaa 60
ctggaatcca teggtcatgc tetegeegaa ccagacatge etettgteet tggggttett 120
gctgatgtac cagttcttct gggccacact gggctgagtg gggtacacgc aggtctcacc 180
agtetecatg ttgcagaaga etttgatgge atecaggttg cageettggt tggggaeetg 240
cccqqqcqqc cqctcqa
<210> 209
<211> 747
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 453, 538, 540, 542, 546, 554, 556, 598, 659, 670, 679, 689,
693, 711, 723, 724, 731, 747
<223> n = A, T, C or G
<400> 209
tegageggee geeegggeag gtecaceaea eceaatteet tgetggtate atggeageeg 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagcccctg 240
attggaagga aaaagacaga cgagetteee caactggtaa ceetteeaca ceecaatett 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt egteaccae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatctt tgaggaacat qqntttaqqc qqaccacacc qcccacaacq 480
gccaccccca taaggcatag gccaagacca tacccgccga atgtaggaca agaagctntn 540
tntcanacac catntnatgg gccccattcc aggacacttc tgagtacatc atttatgnca 600
tetgtggcae ttgatgaaaa eeettacagt teagggttet ggaaetttta eeaggeetnt 660
tacaggactn ggccggacnc cttaagccna ttncaccctg gggcgttcta nggtcccact 720
cgnncactgg ngaaaatggc tactgtn
<210> 210
<211> 872
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 165, 174, 181, 256, 260, 269, 271, 277, 286, 289, 294, 298,
300, 301, 303, 308, 311, 321, 325, 328, 329, 333, 338, 342, 346, 349, 351, 357, 359, 364, 366, 379, 385, 395, 396, 397, 407, 408, 410, 414, 415, 429, 431, 434, 435, 440, 443
<223> n = A, T, C or G
<221> misc feature
<222> 444, 446, 447, 448, 449, 450, 451, 464, 470, 472, 475, 479,
483, 484, 485, 488, 494, 496, 497, 504, 508, 509, 511, 513,
517, 522, 524, 526, 532, 533, 542, 543, 553, 559, 566, 567,
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571, 572, 578, 582, 588, 591, 594, 595, 596, 600, 606
\langle 223 \rangle n = A,T,C or G
<221> misc feature
<222> 612, 614, 617, 618, 629, 630, 631, 652, 654, 655, 661, 663,
664, 666, 671, 673, 678, 679, 681, 688, 690, 691, 698, 706,
707, 708, 714, 719, 721, 723, 726, 741, 751, 761, 762, 769, 770, 778, 779, 781, 782, 785, 791, 802, 807, 808, 812
<223> n = A, T, C or G
<221> misc feature
<222> 815, 820, 827, 828, 838, 841, 844, 851, 857, 864, 866, 869,
<223> n = A, T, C or G
<400> 210
agegtggteg eggeegaggt ceactagagg tetgtgtgee attgeecagg cagagtetet 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgngaaac tccnaggaca 180
ngagggetaa attecatgaa gtttgtggat ggeetgatga tecacaateg gagaceetgt 240
taactactac cgtctnaccn cctgctgtnc ncccccnttt ctgctnaana catngggntn 300
ntnettgnee nteettgggt ngaanatnna atngeetnee enttentane netaetngnt 360
ccananttgg cctttaaana atccnccttg ccttnnncac tgttcanntn tttnntcgta 420
aaccctatna nttnnattan atnntnnnnn nctcacccc ctcntcattn anccnatang 480
ctnnnaantc cttnanncct ccenccennt nenctentac tnantnette tnncccatta 540
cnnagetett tentttaana taatgnngee nngetetnea thtetaenat htgnnnaath 600
ecceences enancgnntt tttgacetnn naaceteett teetetteee tnennaaatt 660
nonnanttee nentteenne nttteggntn nteecatnet tteeannnet teantetane 720
nenetneaac ttattteet nteatecett nttetttaca nnececetnn tetaetenne 780
nnttncatta natttgaaac tnccacnnct anttncctcn ctctacnntt ttattttncg 840
ntcnctctac ntaatanttt aatnanttnt cn
                                                                     872
<210> 211
<211> 517
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 462, 464, 506
<223> n = A, T, C or G
<400> 211
tcgagcggcc gcccgggcag gtctgccaag gagaccctgt tatgctgtgg ggactggctg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtggcag 120
tatctcatct ttgggttcca caatgctcac gtggtcaggc aggggcttct tagggccaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacaa gcagtgtcaa cgtagtaagt taacagggtc tccgctgtgg 300
atcatcaggc catccacaaa cttcatggat ttagccctct gtcctcggag tttcccagac 360
accacaacct cgcagccttt ggccccactc tccatgatga accgcagcac accatagcag 420
gccctccgca caagcaagcc ctcctaagaa tttgtaacgc ananactctg ctggcaatgg 480
cacacaaacc tctagtggac ctcggncgcg accacgc
                                                                     517
<210> 212
<211> 695
<212> DNA
<213> Homo sapiens
```

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<220>
<221> misc feature
<222> 432, 476, 522, 547, 621, 624, 647, 679
<223> n = A, T, C or G
<400> 212
tegageggee geeegggeag gtetggteea ggatageetg eqaqteetee tactgetact 60
ccagacttga catcatatga atcatactgg ggagaatagt tctgaggacc agtagggcat 120
gattcacaga ttccaggggg gccaggagaa ccaggggacc ctggttgtcc tggaatacca 180
gggtcaccat ttctcccagg aataccagga gggcctggat ctcccttggg gccttgaggt 240
ccttgaccat taggagggcg agtaggagca gttggaggct gtgggcaaac tgcacaacat 300
tctccaaatg gaatttctgg gttggggcag tctaattctt gatccgtcac atattatgtc 360
ategeagaga aeggateetg agteaeagae acatatttgg catggttetg getteeagae 420
atctctatcc gncataggac tgaccaagat gggaacatcc tccttcaaca agcttnctgt 480
tgtgccaaaa ataatagtgg gatgaagcag accgagaagt anccagctcc cctttttgca 540
caaagcntca tcatgtctaa atatcagaca tgagacttct ttgggcaaaa aaggagaaaa 600
agaaaaagca gttcaaagta nccnccatca agttggttcc ttgcccnttc agcacccggg 660
ccccgttata aaacacctng ggccggaccc ccctt
<210> 213
<211> 804
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 552, 555, 592, 624, 629, 633, 658, 695, 697, 698, 700, 702,
745, 753, 755, 762, 773, 786, 788, 793, 795
<223> n = A, T, C or G
<400> 213
agegtggteg eggeegaggt gttttatgae gggeeeggtg etgaagggea gggaacaaet 60
tgatggtgct actttgaact gcttttcttt tctccttttt gcacaaagag tctcatgtct 120
gatatttaga catgatgagc tttgtgcaaa aggggagctg gctacttctc gctctgcttc 180
atcccactat tattttggca caacaggaag ctgttgaagg aggatgttcc catcttggtc 240
agtectatge ggatagagat gtetggaage cagaaceatg ceaaatatgt gtetgtgaet 300
caggatccgt tetetgcgat gacataatat gtgacgatca agaattagac tgccccaacc 360
cagaaattcc atttggagaa tgttgtgcag tttgcccaca gcctccaact gctcctactc 420
gecetectaa tggteaagga eeteaaggee eeaagggaga teeaggeeet eetggtatte 480
ctgggagaaa tggtgaccct ggtattccag gacaaccagg gtcccctggt tctcctggcc 540
cccctggaat cnggngaatc atgccctact ggtcctcaaa ctattctccc anatgattca 600
tatgatgtca agtctgggat agcnagtang ganggactcg caggctattc tggaccanac 660
ctgccggggg ggcgttcgaa agcccgaatc tgcananntn cnttcacact ggcggccgtc 720
gagctgcttt aaaagggcca ttccnccttt agngnggggg antacaatta ctnggcggcg 780
ttttanancg cgngnctggg aaat
                                                                  804
<210> 214
<211> 594
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 452, 509, 585
<223> n = A, T, C or G
<400> 214
agegtggteg eggeegaggt.ceacategge agggteggag eeetggeege catactegaa 60
```

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ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
gctgatgtac cagttettet gggccacact gggctgagtg gggtacacgc aggteteacc 180
agtetecatg ttqcagaaga etttqatggc atccaqqttq caqcettqqt tqqqqtcaat 240
ccagtactet ccaetettee agteagagtg geacatettg aggteaegge aggtgeggge 300
ggggttettg eggetgeeet etgggeteeg gatgtteteg atetgetgge teaggetett 360
gagggtggtg tecacetega ggteaeggte aegaaceaea ttggeateat eageeeggta 420
gtagcggcca ccatcgtgag ccttctcttg angtggctgg ggcaggaact gaagtcgaaa 480
ccagcgctgg gaggaccagg gggaccaana ggtccaggaa gggcccgggg gggaccaaca 540
qqaccaqcat caccaaqtqc qaccqqcqaq aacctqcccq qccqnccqct cqaa
<210> 215
<211> 590
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9
<223> n = A,T,C or G
<400> 215
tegagegnne geeegggeag gtetegeggt egeaetggtg atgetggtee tgttggteec 60
cccggccctc ctggacctcc tggtccccct ggtcctccca gcgctggttt cgacttcagc 120
tteetgeece agecacetea agagaagget caegatggtg geegetacta eegggetgat 180
gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagcctgagc 240
cagcagateg agaacateeg gageecagag ggeageegea agaaceeege eegeacetge 300
cgtgacctca agatgtgcca ctctgactgg aagagtggag agtactggat tgaccccaac 360
caaggetgea acctggatge catcaaagte ttetgeaaca tggagactgg tgagacetge 420
gtgtacccca ctcagcccag tgtggcccag aagaactggt acatcagcaa gaaccccaag 480
gacaagaggc atgtctggtt cggcgagagc atgaccgatg gattccagtt cgagtatggc 540
ggccagggct cccaccctgc cgatgtggac ctccggccgc gaccaccctt
                                                                     590
<210> 216
<211> 801
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 2, 2\overline{2}, 25, 26, 328, 373, 385, 440, 473, 534, 571, 572, 573,
582, 587, 589, 593, 600, 605, 617, 633, 642, 653, 672, 681, 685, 696, 699, 709, 715, 717, 726, 731, 739, 742, 745, 758,
769, 772, 778, 780, 788, 789, 791, 793, 796
<223> n = A, T, C or G
<400> 216
tngageggee geeegggeag gntgnnaaeg etggteetge tggteeteet ggeaaggetg 60
gtgaagatgg teaccetgga aaacceggac gacetggtga gagaggagtt gttggaccac 120
agggtgctcg tggtttccct ggaactcctg gacttcctgg cttcaaaggc attaggggac 180
acaatggtet ggatggattg aagggacage ceggtgetee tggtgtgaag ggtgaacetg 240
gtgcccctgg tgaaaatgga actccaggtc aaacaggagc ccgtgggctt cctggtgaga 300
gaggaccgtg ttggtgcccc tggcccanac ctcggccgcg accacgctaa gcccgaattt 360
ccagcacact ggnggccgtt actantggat ccgagctcgg taccaagctt ggcgtaatca 420
tggtcatagc tgtttcctgn gtgaaattgt tatccgctca caatttcaca cancatacga 480
agccggaaag cataaagtgt aaagccttgg ggtgctaatg agtgagctaa ctcncattaa 540
attgcgttgc gctcactgcc cgcttttcca nnngggaaac cntggcntng ccngcttgcn 600
ttaantgaaa teegeenaee eeeggggaaa agneggtttg engtattggg genettttte 660
cetttecteg gnttacttga nttantggge tttggnegnt tegggttgng geganenggt 720
```

```
tcaacntcac nccaaaggng gnaanacggt tttcccanaa tccgggggnt ancccaangn 780
aaaacatnng nenaanggge t
<210> 217
<211> 349
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 10, \overline{1}57, 170
<223> n = A, T, C or G
<400> 217
agegtggttn geggeegagg tetgggeeag gggeaceaac aegteetete teaceaggaa 60
geccaeggge teetgtttga cetggagtte catttteace aggggeacea ggtteaceet 120
teacaceagg ageaeeggge tgteeettea ateeatneag accattgtgn cecetaatge 180
ctttgaagcc aggaagtcca ggagttccag ggaaaccacc gagcaccctg tggtccaaca 240
actectetet caccaggteg teegggtttt ceagggtgac catetteace ageettgeea 300
ggaggaccag caggaccagc gttaccaacc tgcccgggcg gccgctcga
<210> 218
<211> 372
<212> DNA
<213> Homo sapiens
<400> 218
tegageggee geeegggeag gtecatttte teeetgaegg teeeacttet eteeaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagcctaag cactggcaca acagtttaaa gcctgattca gacattcgtt cccactcatc 180
tecaaeggea taatgggaaa etgtgtaggg gteaaageae gagteateeg taggttggtt 240
caageetteg ttgacagagt tgeccacggt aacaacetet teecgaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggaccteggc 360
cgcgaccacg ct
<210> 219
<211> 374
<212> DNA
<213> Homo sapiens
<400> 219
agcgtggtcg cggccgaggt cctcaccaga ggtgccacct acaacatcat agtggaggca 60
ctgaaagacc agcagaggca taaggttcgg gaagaggttg ttaccgtggg caactctgtc 120
aacgaagget tgaaccaace tacggatgac tegtgetttg acccetacac agttteccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttaggct ttggaagtgg tcatttcaag atgtgattca tctagatggt gccatgacaa 300
tggtgtgaac tacaagattg gagagaagtg ggaccgtcag ggagaaaatg gacctgcccg 360
ggccggccgc tcga
                                                                    374
<210> 220
<211> 828
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 8, 9, 557, 571, 587, 588, 601, 642, 643, 647, 654, 664, 681,
688, 698, 719, 720, 725, 734, 738, 743, 744, 757, 765, 773,
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778, 780, 782, 783, 793, 798, 805, 809, 822, 827
<223> n = A, T, C or G
<400> 220
tegagegnne gecegggeag gtecagtagt geetteggga etgggtteae eeceaggtet 60
geggeagttg teacagegee ageecegetg geetecaaag catgtgeagg ageaaatgge 120
accgagatat teettetgee actgttetee tacgtggtat gtetteecat categtaaca 180
cgttqcctca tqaqqqtcac acttqaattc tccttttccq ttcccaaqac atqtqcaqct 240
cattiggctg gctctatagt tiggggaaag titgttgaaa cigtgccact gacctitact 300
tecteettet etactggage tttegtacet tecaettetg etgttggtaa aatggtggat 360
cttctatcaa tttcattgac agtacccact tctcccaaac atccagggaa atagtgáttt 420
cagagcgatt aggagaacca aattatgggg cagaaataag gggcttttcc acaggttttc 480
ctttggagga agatttcagt ggtgacttta aaagaatact caacagtgtc ttcatcccca 540
tagcaaaaga agaaacngta aatgatggaa ngcttctgga qatgccnnca tttaagggac 600
neceagaact teaceateta caggacetae tteagtttae annaagneae atantetgae 660
tcanaaagga cccaagtagc nccatggnca gcactttnag cctttcccct ggggaaaann 720
ttacnttctt aaancctngg conngacccc cttaagncca aattntggaa aanttccntn 780
ennetggggg gengttenac atgentttna agggeceaat tneecent
<210> 221
<211> 476
<212> DNA
<213> Homo sapiens
<400> 221
tegageggee geeegggeag gtgteggagt ceageaeggg aggegtggte ttgtagttgt 60
tctccggctg cccattgctc tcccactcca cggcgatgtc gctgggatag aagcctttga 120
ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtgt 180
acacctgtgg ttctcggggc tqccctttgg ctttggagat ggttttctcg atgggggctg 240
ggagggettt gttggagace ttgcacttgt acteettgce attcagecag teetggtgca 300
ggacggtgag gacgctgacc acacggtacg tgctgttgta ctgctcctcc cqcggctttq 360
tettggcatt atgeacetee acgeegteea egtaceagtt gaacttgace teagggtett 420
cgtggctcac gtccaccacc acgcatgtaa cctcagacct cggccgcgac cacgct
<210> 222
<211> 477
<212> DNA
<213> Homo sapiens
<400> 222
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ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
gccgcgggag gagcagtaca acagcacgta ccgtgtggtc agcgtcctca ccgtcctqca 180
ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag ccctcccagc 240
ccccatcgag aaaaccatct ccaaagccaa agggcaagcc ccgagaacca caggtgtaca 300
ecctgcccc atcccgggag gagatgacca agaaccaggt cagcctgacc tgcctggtca 360
aaggetteta teecagegae ategeegtgg agtgggagag caatgggeag eeggagaaca 420
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<210> 223
<211> 361
<212> DNA
<213> Homo sapiens
<400> 223
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ggtacagage tecgatgggt gaaaccattg acatagagae tgteeetgte cagggtgtag 120
gggcccagct cagtgatgcc gtgggtcagc tggctcagct tccagtacag ccgctctctg 180
```

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tccagtccag ggcttttggg gtcaggacga tgggtgcaga cagcatccac tctggtggct 240
geoccatect teteaggeet gageaaggte agtetgeaac cagagtacag agagetgaca 300
ctggtgttct tgaacaaggg cataagcaga ccctgaagga cacctcggcc gcgaccacgc 360
<210> 224
<211> 361
<212> DNA
<213> Homo sapiens
<400> 224
agcgtggtcg cggccgaggt gtccttcagg gtctgcttat gcccttgttc aagaacacca 60
gtgtcagctc tctgtactct ggttgcagac tgaccttgct caggcctgag aaggatgggg 120
cagecaceag agtggatget gtetgeacec ategteetga ecceaaaage eetggaetgg 180
acagagageg getgtaetgg aagetgagee agetgaeeca eggeateact gagetgggee 240
cctacaccct ggacagggac aqtctctatg tcaatggttt cacccatcgg agctctgtac 300
ccaccaccag caccggggtg gtcagcgagg agccattcaa cctgcccggg cggccgctcg 360
<210> 225
<211> 766
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 574, 610, 631, 643, 657, 660, 666, 688, 712, 735, 747
<223> n = A, T, C or G
<400> 225
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actqtaaggg ttcttcatca qtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
ggtatggtet tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
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gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
ctgtggaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
gttggggaag ctcgtctgtc tttttccttc caatcagggg ctcgctcttc tgattattct 480
teagggeaat gacataaatt gtatattegg teeeggttee aggeeagtaa tagtageete 540
tgtgacacca gggcggggcc gagggaccet tctnttggaa gagaccagct tctcatactt 600
gatgatgagn ccggtaatcc tggcacgtgg nggttgcatg atnccaccaa ggaaatnggn 660
gggggnggac ctgcccggcg gccgttcnaa agcccaattc cacacacttg gnggccgtac 720
tatggatccc actcngtcca acttggngga atatggcata actttt
                                                                   766
<210> 226
<211> 364
<212> DNA
<213> Homo sapiens
<400> 226
togagoggeo geoogggeag gtoottgace ttttcagcaa gtgggaaggt gtaatccgte 60
tccacaqaca aggccaggac tcgtttgtac ccgttgatga tagaatgggg tactgatgca 120
acagttgggt agccaatctg cagacagaca ctggcaacat tgcggacacc ctccaggaag 180
cgagaatgca gagtttcctc tgtgatatca agcacttcag ggttgtagat gctgccattg 240
tcgaacacct gctggatgac cagcccaaag gagaaggggg agatgttgag catgttcagc 300
agogtggett cgctggetcc cactttgtct ccagtcttga tcagacctcg gccgcgacca 360
cact
```

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<211> 275
<212> DNA
<213> Homo sapiens
<400> 227
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gcccagcaac accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac 180
atgcccaccg tgcccagcac ctgaactcct ggggggaccg tcagtcttcc tcttcccccg 240
cateccett ceaaacetge cegggeggee geteg
<210> 228
<211> 275
<212> DNA
<213> Homo sapiens
<400> 228
cgagcggccg cccgggcagg tttggaaggg ggatgcgggg gaagaggaag actgacggtc 60
cccccaggag ttcaggtgct gggcacggtg ggcatgtgtg agttttgtca caagatttgg 120
qctcaactet cttgtccacc ttggtgttgc tgggcttgtg atctacgttg caggtgtagg 180
totggqtgcc gaagttqctq qaqqqcacqq tcaccacqct qctqaqqqaq tagagtcctg 240
aggactgtag gacagacctc ggccgcgacc acgct
<210> 229
<211> 40
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 1, 4, 5, 13, 15, 17, 29
<223> n = A, T, C or G
                                                                   40
nggnnggtec ggnengneag gaecactent ettegaaata
<210> 230
<211> 208
<212> DNA
<213> Homo sapiens
<400> 230
agcgtggtcg cggccgaggt cctcacttgc ctcctgcaaa gcaccgatag ctgcgctctg 60
gaagegeaga tetgttttaa agteetgage aatttetege accagaeget ggaagggaag 120
tttgcgaatc agaagttcag tggacttctg ataacgtcta atttcacgga gcgccacagt 180
accaggacct gcccgggcgg ccgctcga
<210> 231
<211> 208
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 33
<223> n = A, T, C or G
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<400> 231
togagoggco gocogggcag gtoctqqtac tqnqqcqctc cqtqaaatta qacqttatca 60
gaagtccact gaacttctga ttcgcaaact tcccttccag cgtctggtgc gagaaattgc 120
tcaggacttt aaaacagatc tgcgcttcca gagcgcagct atcggtgctt tgcaggaggc 180
aagtgaggac ctcggccgcg accacgct
<210> 232
<211> 332
<212> DNA
<213> Homo sapiens
<400> 232
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aactggaatc categgteat getetegeeg aaccagacat geetettgte ettggggtte 120
ttgctgatgt accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
gcggggttct tgacctcggc cgcgaccacg ct
<210> 233
<211> 415
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 15, 19, 21
<223> n = A, T, C or G
<400> 233
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gccagtgtgc tggaattcgg cttagcgtgg tcgcggccga ggtcaagaac cccgcccgca 120
cctgccgtga cctcaagatg tgccactctg actggaagag tggagagtac tggattgacc 180
ccaaccaagg ctgcaacctg gatgccatca aagtcttctg caacatggag actggtgaga 240
cctgcgtgta ccccactcag cccagtgtgg cccagaagaa ctggtacatc aqcaaqaacc 300
ccaaggacaa gaggcatgtc tggttcggcg agagcatgac cgatggattc cagttcgagt 360
atggcggcca gggctccgac cctgccgatg tggacctgcc cgggcggccg ctcga
<210> 234
<211> 776
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 505, 550, 574, 601, 604, 608, 612, 649, 656, 657, 680, 711,
750, 776
<223> n = A, T, C or G
<400> 234
agegtggteg eggeegaggt etgggatget cetgetgtea eagtgagata ttacaqqate 60
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tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggetge etteaagtte ceetgttaet ggttacagag taaccaccae teecaaaaat 360
ggaccaggac caacaaaaac taaaactgca ggtccagatc aaacagaaat gactattqaa 420
ggcttgcagc ccacagtgga gtatgtggtt aagtgtctat gctcagaatc caagcggaga 480
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gaagtcagcc tetggttcag actgnaagta accaacattg ategeetaaa ggactggcat 540
tcactgatgn ggatgccgat tccatcaaaa ttgnttggga aaacccacag gggcaagttt 600
ncangtonag gnggacctac togagocotg aggatggaat cottgactnt toottnnoot 660
gatggggaaa aaaaaccttn aaaacttgaa ggacctgccc gggcggccgt ncaaaaccca 720
attecacece cttgggggcg ttetatgggn cccactegga ccaaacttgg ggtaan
<210> 235
<211> 805
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 637, 684, 705, 724, 733, 756, 778, 793, 796, 804
<223> n = A,T,C or G
<400> 235
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agggaatage teatggatte catecteagg getegagtag gteaccetgt acctggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg gcatccacat cagtgaatgc 180
cagtccttta gggcgatcaa tgttggttac tgcagtctga accagaggct gactctctcc 240
gcttggattc tgagcataga cactaaccac atactccact gtgggctgca agccttcaat 300
agtcatttct gtttgatctg gacctgcagt tttagttttt gttggtcctg gtccattttt 360
gggagtggtg gttactctgt aaccagtaac aggggaactt gaaggcagcc acttgacact 420
aatgctgttg tcctgaacat cggtcacttg catctgggat ggtttgtcaa tttctgttcg 480
gtaattaatg gaaattggct tgctgcttgc ggggcttgtc tccacggcca gtgacagcat 540
acacagtgat ggtataatca actccaggtt taagccgctg atggtagctg aaactttgct 600
ccaggcacaa gtgaactcct gacaggcta tttcctnctg ttctccgtaa gtgatcctgt 660
aatatctcac tgggacagca ggangcattc caaaacttcg ggcgngaccc cctaagccga 720
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cctataggga gtntantaca attng
<210> 236
<211> 262
<212> DNA
<213> Homo sapiens
<400> 236
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attgtctccc atttttttgg cttttgaggg ggttcagttt gggttgcttg tctgtttccg 180
ggttggggg aaagttggtt gggtgggagg gagccaggtt gggatggagg gagtttacag 240
gaagcagaca gggccaacgt cg
                                                                   262
<210> 237
<211> 372
<212> DNA
<213> Homo sapiens
<400> 237
agegtggteg eggeegaggt ceteaceaga ggtgeeacet acaacateat agtggaggea 60
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aacgaagget tgaaccaacc tacggatgac tegtgetttg accectacac agttteccat 180
tatgccgttg gagatgagtg ggaacgaatg tctgaatcag gctttaaact gttgtgccag 240
tgcttaggct ttggaagtgg tcatttcaga tgtgattcat ctagatggtg ccatgacaat 300
ggtgtgaact acaagattgg agagaagtgg gaccgtcagg gagaaaatgg acctgcccgg 360
                                                                   372
geggeegete ga
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<210> 238
<211> 372
<212> DNA
<213> Homo sapiens
<400> 238
tegagegee geeeggeag gtecatttte teeetgaegg teccaettet etecaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaagectaag cactggcaca acagtttaaa geetgattea gacattegtt eecacteate 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgeceaeggt aacaacetet teeegaacet tatgeetetg 300
ctggtctttc agtgcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcggc 360
cgcgaccacg ct
<210> 239
<211> 720
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 478, 557, 563, 566, 620, 660, 663, 672, 673, 684, 693, 695
<223> n = A, T, C or G
<400> 239
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qqaqcaaqqt tqatttcttt cattggtccg qtcttctcct tgggggtcac ccgcactcga 120
tatecaqtqa qetqaacatt qqqtqqtqtc cactqqqcqc tcaqqettqt qgqtqtqacc 180
tgagtgaact tcaggtcagt tggtgcagga atagtggtta ctgcagtctg aaccagaggc 240
tgactctctc cgcttggatt ctgagcatag acactaacca catactccac tgtgggctgc 300
aagcetteaa tagteattte tgtttgatet ggacetgeag ttttagtttt tgttggteet 360
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cacttgacac taatgetgtt gteetgaaca teggteactt geatetggga tggtttgnca 480
atttctgttc ggtaattaat ggaaattggc ttgctgcttg cggggctgtc tccacggcca 540
gtgacagcat acacagngat ggnatnatca actccaagtt taaggccctg atggtaactt 600
taaacttget eecageeagn gaactteegg acagggtatt tettetggtt tteegaaagn 660
gancetggaa tnnteteett ggancagaag ganenteeaa aacttgggee ggaaceeett 720
<210> 240
<211> 691
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 564, 582, 640, 651, 666, 669, 690
<223> n = A, T, C or G
<400> 240
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actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct acattcggcg 180
 ggtatggtct tggcctatgc cttatggggg tggccgttgt gggcggtgtg gtccgcctaa 240
 aaccatgttc ctcaaagatc atttgttgcc caacactggg ttgctgacca gaagtgccag 300
gaagctgaat accatttcca gtgtcatacc cagggtgggt gacgaaaggg gtcttttgaa 360
 ctqtqqaagg aacatccaag atctctggtc catgaagatt ggggtgtgga agggttacca 420
 qttqqqqaaq ctcgtctgtc tttttccttc caatcagggg ctcgctcttc tgattattct 480
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tcaqqqcaat gacataaatt gtatattcqq ttcccqqttc caqqccaqta ataqtaqcct 540
cttgtgacac caggcggggc ccanggacca cttctctggg angagaccca gcttctcata 600
cttgatgatg taacccggta atcctgcacg tggcggctgn catgatacca ncaaggaatt 660
gggtgnggng gacctgcccg gcggccctcn a
<210> 241
<211> 808
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 680, 715, 721, 728, 735, 749, 757, 762, 772, 776, 779, 781,
792, 796, 800, 808
<223> n = A, T, C or G
<400> 241
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acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
totacagota coatcagogg cottaaacot ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagag taaccaccac tcccaaaaat 360
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ggcttgcagc ccacagtgga gtatgtggtt agtgtctatg ctcagaatcc aagcggagag 480
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acteaggtea cacceacaag cetgageege cagtggacae cacceaatgt teacteactg 600
qatatcqaqt qcqqqtqacc cccaaqqaga aqacccggac ccatgaaaga aatcaacctt 660
gctcctgaca gctcatccgn gggtgtatca ggacttatgg gggactgccc cggcnggccg 720
ntegaaaneg aattntgaaa ttteettene aetgggngge gnttegaget tnettntana 780
nggcccaatt cncctntagn gggtcgtn
<210> 242
<211> 26
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 22
<223> n = A, T, C or G
                                                                   26
agcgtggtcg cggccgaggt cnagga
<210> 243
<211> 697
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 496, 541, 624, 662, 679, 688
<223> n = A, T, C or G
<400> 243
tegageggee geeegggeag gteeaceaca cecaatteet tgetggtate atggeageeg 60
ccacqtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
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gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagccctg 240
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catggaccag agatettgga tgtteettee acagtteaaa agaeceettt egteaceeae 360
cctgggtatg acactggaaa tggtattcag cttcctggca cttctggtca gcaacccagt 420
gttgggcaac aaatgatctt tgaggaacat ggttttaggc ggaccacacc gcccacaacg 480
ggcaccccca taaggnatag gccaagacca taccccgccg aatgtaggac aagaagctct 540
ntetcaacaa ccatetcatg ggececatte caggacactt etgagtacat cattteatgt 600
catcetggtg ggcacttgat gaanaaccet tacagttcag ggttcetgga acttetacca 660
gngccacttc tgacagganc ttgggcgnga ccaccct
<210> 244
<211> 373
<212> DNA
<213> Homo sapiens
<400> 244
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agttcacacc attgtcatgg caccatctag atgaatcaca tctgaaatga ccacttccaa 120
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caacggcata atgggaaact gtgtaggggt caaagcacga gtcatccgta ggttggttca 240
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<210> 245
<211> 307
<212> DNA
<213> Homo sapiens
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cccaacccgg aaacagacaa gcaacccaaa ctgaaccccc tcaaaagcca aaaaaatggg 180
agacaatttc acatggactt tggaaaatat tttttcctt tgcattcatc tctcaaactt 240
agtttttatc tttgaccaac cgaacatgac caaaaaccaa aagtgacctg cccgggegge 300
cgctcqa
                                                                   307
<210> 246
<211> 372
<212> DNA
<213> Homo sapiens
<400> 246
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cactgaaaga ccagcagagg cataaggttc gggaagaggt tgttaccgtg ggcaactctg 120
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attatgccgt tggagatgag tgggaacgaa tgtctgaatc aggctttaaa ctgttgtgcc 240
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atggtgtgaa ctacaagatt ggagagaagt gggaccgtca gggagaaaat ggacctcggc 360
cgcgaccacg ct
<210> 247
<211> 348
<212> DNA
<213> Homo sapiens
<220>
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<221> misc feature
<222> 284, 297, 299, 322, 325, 338, 342, 345
<223> n = A, T, C \text{ or } G
<400> 247
tegageggee geeegggeag gtaceggggt ggteagegag gagecattea caetgaactt 60
caccatcaac aacctgcggt atgaggagaa catgcagcac cctggctcca ggaagttcaa 120
caccacqqaq agggtccttc agggcctgct caggtccctq ttcaaqaqca ccagtqttgg 180
ccctctgtac tctggctgca gactgacttt gctcagacct gagaaacatg gggcagccac 240
tggagtggac gccatctgca ccctccgcct tgatcccact ggtnctggac tggacanana 300
geggetatae ttgggagetg ancenaacet ttggeggnga encenett
<210> 248
<211> 304
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 125
<223> n = A, T, C or G
<400> 248
qaqqactqqc tcaqctccca gtataqccqc tctctqtcca qtccaqqacc aqtqqqatca 60
aggeggaggg tgeagatgge gtecaeteca gtggetgeee catgtttete aagtetgage 120
aaagncagtc tgcagccaga gtacagaggg ccaacactgg tgctcttgaa cagggacctg 180
agcaggccct gaaggaccct ctccgtggtg ttgaacttcc tggagccagg gtgctgcatg 240
ttctcctcat accgcaggtt gttgatggtg aagttcagtg tgaatggctc ctcgctgacc 300
accc
<210> 249
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 308, 310, 312, 320, 331, 336, 383, 392, 396
<223> n = A, T, C or G
<400> 249
agcgtggtcg cggccgaggt ccaccacac caattccttg ctggtatcat ggcagccgcc 60
acgtgccagg attaccggct acatcatcaa gtatgagaag cctgggtctc ctcccagaga 120
agtggtccct cggccccgcc ctggtgtcac agaggctact attactggcc tggaaccggg 180
aaccgaatat acaatttatg tcattgccct gaagaataat cagaagagcg agcccctgat 240
tggaaggaaa aagacagacg agcttcccca actggtaacc cttccacacc ccaatcttca 300
tggaccanan ancttggatn gtcctttcac nggttnaaaa aaccettttc gccccccac 360
cttggggatt aaccttggga aanggggatt tnaccnttcc
<210> 250
<211> 400
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 338, 357, 361, 369, 388, 394
<223> n = A, T, C or G
```

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<400> 250
tegageggee geeegggeag gteetgteag agtggeaetg gtagaagtte caggaaceet 60
gaactgtaag ggttcttcat cagtgccaac aggatgacat gaaatgatgt actcagaagt 120
gtcctggaat ggggcccatg agatggttgt ctgagagaga gcttcttgtc ctacattcgg 180
egggtatggt ettggeetat geettatggg ggtggeegtt gtgggeggtg tggteegeet 240
aaaaccatgt teeteaaaga teatttgttg eecaacaetg ggttgetgae cagaagtgee 300
aggaagctga ataccatttc cagtgtcata cccagggngg gtgaccaaag ggggtcnttt 360
ngacctggng aaaggaacca tccaaaanct ctgncccatg
<210> 251
<211> 514
<212> .DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 8, 107, 312, 338, 351, 352, 357, 363, 366, 373, 380, 405,
421, 444, 508
<223> n = A, T, C or G
<400> 251
agegtggneg eggeegaggt etgaggatgt aaactettee eaggggaagg etgaagtget 60
gaccatggtg ctactgggtc cttctgagtc agatatgtga ctgatgngaa ctgaagtagg 120
tactgtagat ggtgaagtct. gggtgtccct aaatgctgca tctccagagc cttccatcat 180
taccgtttct tcttttgcta tgggatgaga cactgttgag tattctctaa agtcaccact 240
gaaatettee teeaaaggaa aacetqtqqa aaageeeett atttetgeee cataatttqq 300
ttctcctaat cnctctgaaa tcactatttc cctggaangt ttgggaaaaa nngggcnacc 360
tgncantgga aantggatan aaagatccca ccattttacc caacnagcag aaagtgggaa 420
nggtaccgaa aagctccaag taanaaaaag gagggaagta aaggtcaagt gggcaccagt 480
ttcaaacaaa actttcccca aactatanaa ccca
<210> 252
<211> 501
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 20, 21, 25, 44, 343, 347, 356, 362, 387, 391, 398, 409, 428,
430, 453, 494
<223> n = A, T, C or G
<400> 252
aagcggccgc ccgggcaggn ncagnagtgc cttcgggact gggntcaccc ccaggtctgc 60
ggcagttgtc acagcgccag ccccgctggc ctccaaagca tgtgcaggag caaatggcac 120
cgagatattc cttctgccac tgttctccta cqtqqtatqt cttcccatca tcqtaacacq 180
ttgcctcatg agggtcacac ttgaattctc cttttccgtt cccaagacat gtgcagctca 240
tttggctggc tctatagttt ggggaaagtt tgttgaaact gtgccactga cctttacttc 300
ctccttctct actggagctt tccgtacctt ccacttctgc tgntggnaaa aagggnggaa 360
cntcttatca atttcattgg acagtanccc nctttctncc caaaacatnc aagggaaaat 420
attgattnen agageggatt aaggaacaac cenaattatg ggggeeagaa ataaaggggg 480
cttttccaca ggtnttttcc t
<210> 253
<211> 226
<212> DNA
<213> Homo sapiens
```

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<400> 253
tcgagcggcc gcccgggcag gtctgcaggc tattgtaagt gttctgagca catatgagat 60
aacctgggcc aagctatgat gttcgatacg ttaggtgtat taaatgcact tttgactgcc 120
atctcagtgg atgacagcct tctcactgac agcagagatc ttcctcactg tgccagtggg 180
caggagaaag agcatgctgc gactggacct cggccgcgac cacgct
<210> 254
<211> 226
<212> DNA
<213> Homo sapiens
<400> 254
agegtggteg eggeegaggt ceagtegeag catgetettt eteetgeeca etggeacagt 60
gaggaagatc tctgctgtca gtgagaaggc tgtcatccac tgagatggca gtcaaaagtg 120
catttaatac acctaacqta tcgaacatca tagcttggcc caggttatct catatgtgct 180
cagaacactt acaatagcct gcagacctgc ccgggcggcc gctcga
<210> 255
<211> 427
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 327, 403
<223> n = A, T, C or G
<400> 255
egageggeeg eeegggeagg teeagaetee aateeagaga accaceaage eagatgteag 60
aagctacacc atcacaggtt tacaaccagg cactgactac aagatctacc tgtacacctt 120
gaatgacaat gctcggagct cccctgtggt catcgacgcc tccactgcca ttgatgcacc 180
atecaacetg cgtttectgg ccaccacace caatteettg etggtateat ggcageegee 240
acgtgccagg attaccggct acatcatcaa gtatgagaag cctgggtctc ctcccagaga 300
agtggtccct cggccccgcc ctggtgncac agaagctact attactggcc tggaaccggg 360
aaccgaatat acaatttatg tcattgccct gaagaataat canaagagcg agcccctgat 420
tggaagg
<210> 256
<211> 535
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 347, 456, 475
<223> n = A, T, C or G
<400> 256
agcgtggtcg cggccgaggt cctgtcagag tggcactggt agaagttcca ggaaccctga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagtgt 120
cctggaatgg ggcccatgag atggttgtct gagagagagc ttcttgtcct gtctttttcc 180
ttccaatcag gggctcgctc ttctgattat tcttcagggc aatgacataa attgtatatt 240
eggtteeegg tteeaggeea gtaatagtag cetetgtgae accagggegg ggeegaggga 300
ccacttctct gggaggagac ccaggettct catacttgat gatgtanccg gtaatcctgg 360
caccgtggcg gctgccatga taccagcaag gaattgggtg tggtggccaa gaaacgcagg 420
ttggatggtg catcaatggc agtggaggcg tcgatnacca caggggagct ccgancattg 480
tcattcaagg tggacaggta gaatcttgta atcaggtgcc tggtttgtaa acctg
```

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<210> 257
<211> 544
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 495, 511
<223> n = A, T, C or G
<400> 257
tegageggee geeegggeag gtttegtgae egtgaceteg aggtggaeae eacceteaag 60
agectgagec ageagatega gaacateegg ageccagagg geageegeaa gaaceeegee 120
cgcacctgcc gtgacctcaa gatgtgccac tctgactgga agagtggaga gtactggatt 180
qaccccaacc aaggetgeaa cetggatgec atcaaagtet tetgeaacat ggagaetggt 240
gagacetgeg tgtaceceae teageceagt gtggeeeaga agaactggta cateageaag 300
aaccccaagg acaagaagca tgtctggttc ggcgaaagca tgaccgatgg attccagttc 360
gagtatggeg gecagggete egaceetgee gatgtggaee teggeegega eeaegetaag 420
cccgaattcc agcacactgg cggccgttac tagtgggatc cgagcttcgg taccaagctt 480
qqcqtaatca tqqqncataq ctqtttcctq nqtqaaaatq qtattccqct tcacaatttc 540
                                                                   544
ccac
<210> 258
<211> 418
<212> DNA
<213> Homo sapiens
<400> 258
agegtggteg eggeegaggt ceacategge agggteggag eeetggeege catactegaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
qctgatqtac caqttcttct gggccacact gggctgagtg gggtacacgc aggtctcacc 180
agtotocatg ttgcagaaga ctttgatggc atccaggttg cagcottggt tggggtcaat 240
ccagtactet ccaetettee agteagagtg geacatettg aggteaegge aggtgeggge 300
ggggttettg eggetgeet etgggeteeg gatgtteteg atetgetgge teaagetett 360
gaagggtggt gtccacctcg aggtcacggt cacgaaacct gcccgggcgg ccgctcga
<210> 259
<211> 377
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 320, 326, 342, 352
<223> n = A, T, C or G
<400> 259
agegtggteg eggeegaggt caagaaceee geeegeaeet geegtgaeet caagatgtge 60
cactetgact ggaagagtgg agagtactgg attgacccca accaaggetg caacetggat 120
gccatcaaag tcttctgcaa catggagact ggtgagacct gcgtgtaccc cactcagccc 180
agtgtggccc agaagaactg gtacatcagc aagaacccca aggacaagag gcatgtctgg 240
ttcggcgaga gcatgaccga tggattccag ttcgagtatg gcggccaggg ctccgaccct 300
gccgatgtgg acctgcccgn gccggnccgc tcgaaaagcc cnaatttcca gncacacttg 360
gccggccgtt actactg
<210> 260
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<211> 332

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<212> DNA
<213> Homo sapiens
<400> 260
tegageggee geeegggeag gteeacateg geagggtegg ageeetggee geeatacteg 60
aactggaatc catcggtcat gctctcgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgt accagttett etgggeeaca etgggetgag tggggtacae geaggtetea 180
ccagtctcca tgttgcagaa gactttgatg gcatccaggt tgcagccttg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
geggggttet tgacetegge egegaceaeg et
<210> 261
<211> 94
<212> DNA
<213> Homo sapiens
<400> 261
tttttttt tttttttt tttttttt
<210> 262
<211> 650
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 412, 582, 612, 641, 646
<223> n = A, T, C or G
agegtggteg eggeegaggt etggeattee ttegaettet etceageega getteeeaga 60
acatcacata tcactgcaaa aatagcattg catacatgga tcaggccagt ggaaatgtaa 120
agaaggccct gaagctgatg gggtcaaatg aaggtgaatt caaggctgaa ggaaatagca 180
aattcaccta cacagttctg gaggatggtt gcacgaaaca cactggggaa tggagcaaaa 240
caqtctttqa atatcqaaca cgcaaggctg tgagactacc tattgtagat attgcaccct 300
atgacattgg tggtcctgat caagaatttg gtgtggacgt tggccctgtt tgcttttat 360
aaaccaaact ctatctgaaa tcccaacaaa aaaaatttaa ctccatatgt gntcctcttg 420
ttctaatctt ggcaaccagt gcaagtgacc gacaaaattc cagttattta tttccaaaat 480
gtttggaaac agtataattt gacaaagaaa aaaggatact tetetttttt tggetggtee 540
accaaataca attcaaaagg ctttttggtt ttattttttt anccaattcc aatttcaaaa 600
tgtctcaatg gngcttataa taaaataaac tttcaccctt nttttntgat
                                                                650
<210> 263
<211> 573
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 453, 458, 544
<223> n = A, T, C or G
<400> 263
agegtggteg eggeegaggt etgggatget eetgetgtea eagtgagata ttacaggate 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
```

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gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact ggttacagaa gtaaccacca ctcccaaaaa 360
tggaccagga ccaacaaaaa ctaaaactgc aggtccagat caaacagaaa atggactatt 420
gaaggettge ageecacagt ggaagtatgt ggntaggngt etatgeteag aateecaage 480
cggagaaagt cagcettetg gtttagactg cagtaaccaa cattgatege cetaaaggae 540
tggncattca cttggatggt ggatgtccaa ttc
<210> 264
<211> 550
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 39, \overline{1}74, 352, 526
<223> n = A, T, C or G
<400> 264
tegageggee geeegggeag gteettgeag etetgeagng tettetteae cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaccetgt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagngaatgc 180
cagteettta gggegateaa tgttggttae tgeagtetga. accagagget gaetetetee 240
gettggatte tgageataga cactaaceae atactecaet gtgggetgea ageetteaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tggtggtcct gncccatttt 360
tgggaagtgg ggggttactc tgtaaccagt aacaggggaa cttgaaggca gccacttgac 420
actaatgctg ttgtcctgaa catcggtcac ttgcatctgg ggatggtttt gacaatttct 480
ggttcggcaa attaatggaa attggcttgc tgcttggcgg ggctgnctcc acgggccagt 540
gacagcatac
<210> 265
<211> 596
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 347, 352, 353, 534, 555, 587
<223> n = A, T, C or G
<400> 265
tegageggee geeegggeag gteettgeag etetgeagtg tettetteac cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaecetgt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagtgaatgc 180
cagteettta gggegateaa tqttggttae tqeagtetga accaqagget qactetetee 240
gettggatte tgageataga eactaaceae atacteeaet gtgggetgea ageetteaat 300
agtcatttct gtttgatctg gacctgcagt tttaagtttt tgttggncct gnnccatttt 360
tggggaaggg gtggttactc ttgtaaccag taacagggga acttgaagca gccacttgac 420
actaatgctg gtggcctgaa catcggtcac ttgcatctgg gatggtttgg tcaatttctg 480
ttcggtaatt aatgggaaat tqqcttactq qcttqcqqqq qctqtctcca cqqncaqtqa 540
caagcataca caggngatgg gtataatcaa ctccaggttt aaggccnctg atggta
<210> 266
<211> 506
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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<222> 393, 473
<223> n = A, T, C \text{ or } G
<400> 266
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agtaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaagttc ccctgttact gqttacagag taaccaccac tcccaaaaat 360
gggaccagga ccaacaaaaa actaaaactg canggtccag atcaaacaga aatgactatt 420
gaaggettge ageceacagt ggagtatgtg ggttagtgte tatgeteaga atneeaageg 480
gagagagtca gcctctggtt cagact
<210> 267
<211> 548
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 346, 358, 432, 510, 512
<223> n = A, T, C or G
<400> 267
tegageggee geoogggeag gteagegete teaggaegte accaccatgg cetgggetet 60
qctcctcctc accctcctca ctcagggcac agggtcctgg gcccagtctg ccctgactca 120
geotecetee gegteegggt etectggaca gteagteace ateteetgea etggaaccag 180
cagtgacgtt ggtgcttatg aatttgtctc ctggtaccaa caacacccag gcaaggcccc 240
caaactcatg atttctgagg tcactaagcg gccctcaggg gtccctgatc gcttctctgg 300
ctccaagtct ggcaacacgg cctccctgac cgtctctggg ctccangctg aggatgangc 360
tgattattac tggaagctca tatgcaggca acaacaattg ggtgttcggc ggaagggacc 420
aagetqaeeq tnetaaqqte aageceaagg ettqeeece teggteacte tgtteecace 480
ctcctctgaa gaagctttca agccaacaan gncacactgg gtgtgtctca taagtggact 540
ttctaccc
<210> 268
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 98, 380, 421, 454, 495, 506, 512, 561, 565, 579
<223> n = A, T, C or G
agcqtgqtcq cgqccqagqt ctgtagcttc tqtgggactt ccactgctca ggcqtcaggc 60
tcaggtagct gctggccgcg tacttgttgt tgctttgntt ggagggtgtg gtggtctcca 120
etecegeett gaegggetg etatetgeet tecaggeeae tgteaegget eeegggtaga 180
agtcacttat gagacacacc agtgtggcct tgttggcttg aagctcctca gaggagggtg 240
ggaacagagt gaccgagggg gcagccttgg gctgacctag gacggtcagc ttggtccctc 300
egecgaacae ecaattgttg ttgeetgeat atgagetgea gtaataatea geeteateet 360
cagectggag cecagagaen gteaagggag geeegtgttt geeaagaett ggaageeaga 420
naagcgatca qggacccctg agggccgctt tacngacctc aaaaaatcat gaatttqggg 480
ggcctttgcc tgggngttgg ttggtnacca gnaaaacaaa atttcataaa gcaccaacgt 540
cactgctggt ttccagtgca ngaanatggt gaactgaant gtcc
                                                                    584
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<210> 269
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 265, 329
<223> n = A, T, C or G
<400> 269
agegtggteg eggeegaggt ceageateag gageeeegee ttgeeggete tggteatege 60
ctttctttt gtggcctgaa acgatgtcat caattcgcag tagcagaact gccgtctcca 120
ctqctqtctt ataaqtctqc agcttcacag ccaatggctc ccatatgccc agttccttca 180
tqtccaccaa agtacccgtc tcaccattta caccccaggt ctcacagttc tcctgggtgt 240
gettggcccg aagggaggta agtanacgga tggtgctggt cccacagttc tggatcaggg 300
tacgaggaat gacctctagg gcctgggcna caagccctgt atggacctgc ccgggcgggc 360
ccgctcga
<210> 270
<211> 368
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 54, 163, 219, 229, 316
<223> n = A, T, C or G
<400> 270
tegageggee geegggeag greeataeag ggergtrace caggeectag aggneattee 60
ttgtaccctg atccagaact gtgggaccag caccatccgt ctacttacct cccttcgggc 120
caagcacacc caggagaact gtgagacctg gggtgtaaat ggngagacgg gtactttggt 180
qqacatqaaq qaactqqqca tatqqqaqcc attgqctqnq aagctqcana cttataagac 240
agcagtggag acggcagttc tgctactgcg aattgatgac atcgtttcag gccacaaaaa 300
gaaaggcgat gaccanagcc ggcaaggcgg ggcttcctga tgctggacct cggccgccga 360
ccacgctt
<210> 271
<211> 424
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 279, 329, 362, 384, 400
<223> n = A, T, C or G
<400> 271
agegtggteg eggeegaggt ceactagagg tetgtgtgee attgceeagg cagagtetet 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 180
gagggctaaa tccatgaagt ttgtggatgg cctgatgatc cacageggag accctgttaa 240
ctactacgtt gacactgctg tgcgccacgt gttgctcana cagggtgtgc tgggcatcaa 300
ggtgaagatc atgctgccct gggacccanc tggcaaaaat ggcccttaaa aaccccttgc 360
entgaccacg tgaaccattt gtgngaacce caagatgaan atacttgeec accaccecc 420
attc
```

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<210> 272
<211> 541
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 422, 442, 510, 513, 515, 525
<223> n = A, T, C or G
<400> 272
tegageggee geeegggeag gtetgeeaag gagaceetgt tatgetgtgg ggaetggetg 60
gggcatggca ggcggctctg gcttcccacc cttctgttct gagatggggg tggtgggcag 120
tateteatet ttgggtteea caatgeteac gtggteagge aggggettet tagggeeaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacag cagtgtcaac gtagtagtta acagggtctc cgctgtggat 300
catcaggcca tocacaaact toatggattt agocototgt cotoggagtt toccaaaaca 360
ccacaacete gecageettt gggeeceaet tetteatgaa tgaaacegea geacaceatt 420
ancaaggee tteegeacag gnaageett eetaaggagt tttgtaaaeg caaaaaaete 480
ttgcctgggg caaatgggca cacagacctn tantnggacc ttggnccgcg aaccaccgct 540
t
<210> 273
<211> 579
<212> DNA -
<213> Homo sapiens
<220>
<221> misc feature
<222> 223, 265, 277, 308, 329, 346, 360, 366, 429, 448, 517, 524,
531, 578
<223> n = A, T, C or G
<400> 273
agegtggteg eggeegaggt etggeeetee tggeaagget ggtgaagatg gteaceetgg 60
aaaacccgga cgacctggtg agagaggagt tgttggacca cagggtgctc gtggtttccc 120
tggaactcct ggacttcctg gcttcaaagg cattagggga cacaatggtc tggatggatt 180
gaagggacag cccggtgctc ctggtgtgaa gggtgaacct ggngcccctg gtgaaaatgg 240
aactccaggt caaacaggag cccgngggct tcctggngag agaggacgtg ttggtgcccc 300
tggcccanac ctgcccgggc ggccgctcna aaagccgaaa tccagnacac tggcggccgn 360
tactantgga atccgaactt cggtaccaaa gcttggccgt aatcatggcc atagcttgtt 420
ccctggggng gaaattggta ttccgctncc aattccacac aacataccga acccggaaag 480
cattaaagtg taaaagccct gggggggcct aaatgangtg agcntaactc ncatttaatt 540
ggcgttgcgc ttcactgccc cgcttttcca gtccgggna
<210> 274
<211> 330
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 171
<223> n = A, T, C or G
<400> 274
tegageggee geeegggeag gtetgggeea ggggeaceaa caegteetet eteaceagga 60
agcccacggg ctcctgtttg acctggagtt ccattttcac caggggcacc aggttcaccc 120
```

```
ttcacaccag gagcaccggg ctgtcccttc aatccatcca gaccattgtg ncccctaatg 180
cetttgaage caggaagtee aggagtteea gggaaaceae gageaceetg tggtccaaca 240
actectetet caccaggteg teegggtttt ecagggtgae catetteace ageettgeea 300
ggagggccag acctcggccg cgaccacgct
<210> 275
<211> 97
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 35, 72
<223> n = A, T, C or G
<400> 275
ancettegtes eggeogaget ceteaceaga getencacet acaacateat agtegageca 60
ctgaaagacc ancagaggca taaggttcgg gaagagg
<210> 276
<211> 610
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 358, 360, 363, 382, 424, 433, 464, 468, 477, 491, 499, 511,
558, 584, 588, 590
<223> n = A, T, C or G
<400> 276
tegageggee geoegggeag gtecatttte teeetgaegg teceaettet etecaatett 60
gtagttcaca ccattgtcat ggcaccatct agatgaatca catctgaaat gaccacttcc 120
aaaqcctaaq cactqqcaca acaqtttaaa qcctqattca gacattcqtt cccactcatc 180
tccaacggca taatgggaaa ctgtgtaggg gtcaaagcac gagtcatccg taggttggtt 240
caageetteg ttgacagagt tgtecaeggt aacaacetet teeegaacet tatgeetetg 300
ctqqtctttc aqtqcctcca ctatgatgtt gtaggtggca cctctggtga ggacctcngn 360
congaacaac gottaagcoc gnattotgoa gaataatcoc atcacacttg goggoogctt 420
cgancatgca tentaaaagg ggccccaatt tececettat aagngaance gtatttneca 480
atttcactgg necegecgnt tttacaaacg neggtgaact ggggaaaaac cetggeggtt 540
acceaacttt aatcgccntt ggcagcacaa tccccccttt tcgnccancn tgggcgtaaa 600
taaccgaaaa
                                                                   610
<210> 277
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature.
<222> 2, 5, 18, 21, 31
<223> n = A, T, C or G
<400> 277
ancgnggtcg cggccgangt nttttttctt ntttttt
                                                                   38
<210> 278
<211> 443
```

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```
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 156, 212, 233, 245, 327, 331, 336, 361, 364, 381, 391, 397,
\langle 223 \rangle n = A, T, C or G
<400> 278
agcgtggtcg cggccgaggt ctgaggttac atgcgtggtg gtggacgtga gccacgaaga 60
ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg ccaagacaaa 120
gccgcgggag gagcagtaca acagcacgta ccgggnggtc agcgtcctca ccgtcctgca 180
ccagaattgg ttgaatggca aggagtacaa gngcaaggtt tccaacaaag ccntcccagc 240
ccccntcgaa aaaaccattt ccaaagccaa agggcagccc cgagaaccac aggtgtacac 300
cctgcccca tcccgggagg aaaagancaa naaccnggtt cagccttaac ttgcttggtc 360
naangetttt tateeeaaeg naetteeeee ntggaantgg gaaaaaeeaa tgggeeaane 420
cgaaaaacaa ttacaanaac ccc
                                                                     443
<210> 279
<211> 348
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 219, 256, 291, 297, 307, 314, 317
<223> n = A, T, C or G
<400> 279
tcgagcggcc gcccgggcag gtgtcggagt ccagcacggg aggcgtggtc ttgtagttgt 60
tetecgqetq eccattqete teccaeteca eggegatgte getgggatag aageetttga 120
ccaggcaggt caggctgacc tggttcttgg tcatctcctc ccgggatggg ggcagggtga 180
acacctgggg ttctcggggc ttgccctttg gttttgaana tggttttctc gatgggggct 240
ggaagggett tgttgnaaac ettgcaettg acteettgee atteacceag neetggngea 300
ggacggngag gacnetnace acacggaace gggetggtgg actgetee
<210> 280
<211> 149
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 18, \overline{3}4, 51, 118, 120, 140
<223> n = A, T, C or G
<400> 280
agegtggteg eggaegangt cetgteagag tggnaetggt agaagtteea ngaaceetga 60
actgtaaggg ttcttcatca gtgccaacag gatgacatga aatgatgtac tcagaagngn 120
cctggaatgg ggcccatgan atggttgcc
<210> 281
<211> 404
<212> DNA
<213> Homo sapiens
<220>
```

```
<221> misc_feature
<222> 383, 386, 388, 393
<223> n = A, T, C or G
<400> 281
tegageggee geeegggeag gtecaccaca cecaatteet tgetggtate atggeageeg 60
ccacqtqcca qqattaccqq ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaagaata atcagaagag cgagccctg 240
attggaagga aaaagacaga cgagcttccc caactggtaa cccttccaca ccccaatctt 300
catggaccag agatettgga tgtteettee acagtteaaa agacceettt eggeacceec 360
cctgggtatg aacctgggaa aanggnantt aanctttcct ggca
<210> 282
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 320, 341, 424, 450, 459, 487, 498
<223> n = A, T, C or G
<400> 282
agcgtggtcg cggccgaggt ctgggatgct cctgctgtca cagtgagata ttacaggatc 60
acttacggag aaacaggagg aaatagccct gtccaggagt tcactgtgcc tgggagcaag 120
tctacagcta ccatcagcgg ccttaaacct ggagttgatt ataccatcac tgtgtatgct 180
gtcactggcc gtggagacag ccccgcaagc agcaagccaa tttccattaa ttaccgaaca 240
gaaattgaca aaccatccca gatgcaagtg accgatgttc aggacaacag cattagtgtc 300
aagtggctgc cttcaaggtn ccctggtact gggttacaga ntaaccacca ctcccaaaaa 360
tggaccagga accacaaaaa cttaaactgc agggtccaga tcaaaacaga aatgactatt 420
gaangettge ageceaeagt gggagtatgn gggtagtgne tatgetteag aateeaageg 480
gaaaaangtc aagccttntg ggttcaa
<210> 283
<211> 325
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 216, 292, 303, 304
<223> n = A, T, C or G
<400> 283
tegageggee geeegggeag gteettgeag etetgeagtg tettetteac cateaggtge 60
agggaatage teatggatte cateeteagg getegagtag gteaccetgt acetggaaac 120
ttgcccctgt gggctttccc aagcaatttt gatggaatcg acatccacat cagtgaatgc 180
cagteettta gggegateaa tgttggttae tgeagnetga accagagget gaetetetee 240
gettggatte tgageataga cactaaceae atacteeaet gtgggetgea ancetteaat 300
aanncatttc tgtttgatct ggacc
                                                                    325
 <210> 284
 <211> 331
 <212> DNA
 <213> Homo sapiens
 <220>
```

```
<221> misc feature
 <222> 54, 59, 63, 121, 312, 327
 <223> n = A, T, C or G
 <400> 284
 tegageggee geeegggeag gtetggtggg gteetggeae aegeacatgg gggngttgnt 60
 ctnatccagc tgcccagccc ccattggcga gtttgagaag gtgtgcagca atgacaacaa 120
 naccttegac tetteetgee acttetttge cacaaagtge accetggagg geaccaagaa 180
 gggccacaag ctccacctgg actacatogg gccttgcaaa tacatccccc cttgcctgga 240
 ctctgagetg accgaattce cccttgcgca tgcgggactg gctcaagaac cgtcctggca 300
 cccttgtatg anagggatga agacacnacc c
 <210> 285
 <211> 509
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> 316, 319, 327, 329, 339, 344, 357, 384, 398, 427, 443, 450,
 \langle 223 \rangle n = A, T, C or G
 <400> 285
 agegtggteg eggeegaggt etgteetaea gteeteagga etetaeteee teageagegt 60
 ggtgaccgtg ccctccagca acttcggcac ccagacctac acctgcaacg tagatcacaa 120
 gcccagcaac accaaggtgg acaagagagt tgagcccaaa tcttgtgaca aaactcacac 180
 atgcccaccg tgcccagcac ctgaactcct ggggggaccg tcagtcttcc tcttcccccg 240
 catccccctt ccaaacctgc ccgggcggcc gctcgaaagc cgaattccag cacactggcg 300
 gccggtacta gtggancena acttggnanc caacctggng gaantaatgg gcataanctg 360
 tttctggggg gaaattggta tccngtttac aattcccnca caacatacga gccggaagca 420
 taaaagngta aaagcctggg ggnggcctan tgaagtgaag ctaaactcac attaattngc 480
 gttgccgctc actggcccgc ttttccagc
                                                                     509
 <210> 286
 <211> 336
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> 188, 251, 267
. <223 > n = A, T, C \text{ or } G
 <400> 286
 tcgagcggcc gcccgggcag gtttggaagg gggatgcggg ggaagaggaa gactgacggt 60
 cccccagga gttcaggtgc tgggcacggt gggcatgtgt gagttttgtc acaagatttg 120
 ggctcaactc tcttgtccac cttggtgttg ctgggcttgt gatctacgtt gcaggtgtag 180
 gtctgggngc cgaagttgct ggagggcacg gtcaccacgc tgctgaggga gtagagtcct 240
 gaggactgta ngacagacct cggccgngac cacgctaagc cgaattctgc agatatccat 300
 cacactggcg gccgctccga gcatgcattt tagagg
 <210> 287
 <211> 30
 <212> DNA
 <213> Homo sapiens
 <220>
```

```
<221> misc feature
<222> 8, 18
\langle 223 \rangle n \approx A,T,C or G
<400> 287
agcgtggncg cggacganga caacaaccc
                                                                    30
<210> 288
<211> 316
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 22, 130
\langle 223 \rangle n = A, T, C or G
<400> 288
tegageggee geeegggeag gnecacateg geagggtegg agecetggee geeatacteg 60
aactggaatc catcggtcat gctcttgccg aaccagacat gcctcttgtc cttggggttc 120
ttgctgatgn accagttctt ctgggccaca ctgggctgag tggggtacac gcaggtctca 180
ccagteteca tgttgcagaa gaetttgatg gcatecaggt tgcageettg gttggggtca 240
atccagtact ctccactctt ccagtcagag tggcacatct tgaggtcacg gcaggtgcgg 300
gcggggttct tgacct
<210> 289
<211> 308
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 36, 165, 191, 195, 218, 235
<223> n = A, T, C or G
<400> 289
agegtggteg eggeegaggt ceageetgga gataanggtg aaggtggtge eeeeggactt 60
ccaggtatag ctggacctcg tggtagccct ggtgagagag gtgaaactgg ccctccagga 120
cctgctggtt tccctggtgc tcctggacag aatggtgaac ctggnggtaa aggagaaaga 180
ggggctccgg ntganaaagg tgaaggaggc cctcctgnat tggcaggggc cccangactt 240
agaggtggag ctggcccccc tggccccgaa ggaggaaagg gtgctgctgg tcctcctggg 300
ccacctgg
<210> 290
<211> 324
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 184
<223> n = A, T, C or G
<400> 290
tegageggee geeegggeag gtetgggeea ggaggaceaa taggaceagt aggaceett 60
gggccatctt tccctgggac accatcagca cctggaccgc ctggttcacc cttgtcaccc 120
tttggaccag gacttccaag acctcctctt tctccaggca ttccttgcag accaggagta 180
ccancagcac caggtggccc aggaggacca gcagcaccct ttcctccttc gggaccaggg 240
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```
ggaccagete cacetetaag teetggggee cetgecaate caggagggee teetteacet 300
ttctcacccg gagcccctct ttct
<210> 291
<211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 249, 267
<223> n = A,T,C or G
<400> 291
tcgagcggcc gcccgggcag gtccaccggg atattcgggg gtctggcagg aatgggaggc 60
atccagaacg agaaggagac catgcaaagc ctgaacgacc gcctggcctc ttacctggac 120
agagtgagga gcctggagac cgacaaccgg aggctggaga gcaaaatccg ggagcacttg 180
gagaagaagg gaccccaggt cagagactgg agccattact tcaagatcat cgaggacctg 240
agggeteana tettegeaaa taetgengae aatgeeeg
                                                               278
<210> 292
<211> 299
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 6, 19, 25, 51, 53, 61, 63, 70, 109, 136, 157, 241, 276
<223> n = A,T,C or G
<400> 292
atgcgnggtc gcggccgang accanctctg gctcatactt gactctaaag ncntcaccag 60
nanttacggn cattgccaat ctgcagaacg atgcgggcat tgtccgcant atttgcgaag 120
atctgagccc tcaggncctc gatgatcttg aagtaanggc tccagtctct gacctggggt 180
ccettettet ecaagtgete ceggattttg etetecagee teeggttete ggtetecaag 240
netteteact etgtecagga aaagaggeca ggeggnegat cagggetttt geatggaet 299
<210> 293
<211> 101
<212> DNA
<213> Homo sapiens
<400> 293
ttttttttt ttttttt tttttttt ttttttt t
                                                               101
<210> 294
<211> 285
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 64, 103, 110, 237, 282
<223> n = A, T, C or G
<400> 294
tcgagcggcc gcccgggcag gtctgccaac accaagattg gccccggccg catccacaca 60
```

```
gttngtgtgc ggggaggtaa caagaaatac cgtgccctga ggntggacgn ggggaatttc 120
teetgggget cagagtgttg tactegtaaa acaaggatea tegatgttgt etacaatgea 180
tctaataacg agctggttcg taccaagacc ctggtgaaga attgcatcgt gctcatngac 240
agcacaccgt accgacagtg ggtaccgaag tcccactatg cncct
<210> 295
<211> 216
<212> DNA
<213> Homo sapiens
<400> 295
togagoggeo geoogggeag gtocaccaca cocaattoot tgotggtato atggeageog 60
ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc tcctcccaga 120
gaagtggtcc ctcggccccg ccctggtgtc acagaggcta ctattactgg cctggaaccg 180
ggaaccgaat atacaattta tgtcattgcc ctgaag.
<210> 296
<211> 414
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 7, 10, 33, 61, 62, 63, 88, 109, 122, 255, 298, 307, 340,
355, 386, 393
<223> n = A,T,C or G
<400> 296
agegtgnten eggeegagga tggggaaget egnetgtett ttteetteea ateagggget 60
nnntcttctg attattcttc agggcaanga cataaattgt atattcggnt cccggttcca 120
gnccagtaat agtagcctct gtgacaccag ggcggggccg agggaccact tctctgggag 180
gagacccagg etteteatae ttgatgatga ageeggtaat eetggeaegt gggeggetge 240
catgatacca ccaangaatt gggtgtggtg gacctgcccg ggcgggccgc tcgaaaancc 300
gaattentge aagaatatee ateacacttg ggegggeegn tegaaccatg catentaaaa 360
gggccccaat ttccccccta ttaggngaag ccncatttaa caaattccac ttgg
<210> 297
<211> 376
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 312, 326, 335, 361
<223> n = A, T, C or G
<400> 297
tegageggee geeegggeag gtetegeggt egeaetggtg atgetggtee tgttggteec 60
eceggecete etggacetee tggteeceet ggteeteeca gegetggttt egaetteage 120
tteetgeece agecacetea agagaagget caegatggtg geegetacta eegggetgat 180
gatgccaatg tggttcgtga ccgtgacctc gaggtggaca ccaccctcaa gagccttgag 240
ccagcagaat cgaaaacatt cggaacccaa gaagggcaag cccgcaaaga aaccccgccc 300
gcacctggcc gngaacctcc aagaangtgc ccacntcttg actgggaaaa aaagggaaaa 360
ntacttggaa ttggac
<210> 298
<211> 357
<212> DNA
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<213> Homo sapiens
<220>
<221> misc_feature
<222> 345, 346
<223> n = A,T,C or G
<400> 298
agcgtggtcg cggccgaggt ccacatcggc agggtcggag ccctggccgc catactcgaa 60
ctggaatcca tcggtcatgc tctcgccgaa ccagacatgc ctcttgtcct tggggttctt 120
getgatgtac cagttettet gggccacaet gggctgagtg gggtacaege aggteteaec 180
agtctccatg ttgcagaaga ctttgatggc atccaggttg cagccttggt tggggtcaat 240
ccagtactet ccaetettee agteagaagt ggeacatett gaggteaegg cagggtgegg 300
gcggggttct tgcgggctgc ccttctgggc tcccggaatg ttctnngaac ttgctgg
<210> 299
<211> 307
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 281, 285, 306
<223> n = A, T, C or G
<400> 299
agcgtggtcg cggccgaggt ccactagagg tctgtgtgcc attgcccagg cagagtctct 60
gcgttacaaa ctcctaggag ggcttgctgt gcggagggcc tgctatggtg tgctgcggtt 120
catcatggag agtggggcca aaggctgcga ggttgtggtg tctgggaaac tccgaggaca 180
qaqqqctaaa tccatqaaqt ttqtqqatqq cctqatqatc cacaqcqqaq accctqttaa 240
ctactacgtt gacacttgct tgtgcgccac gtgttgctca nacangggtg ggctgggcat 300
caaggng
<210> 300
<211> 351
<212> DNA
<213> Homo sapiens
<400> 300
tegageggee geeegggeag gtetgeeaag gagaceetgt tatgetgtgg ggaetggetg 60
gggcatggca ggcggctetg gcttcccacc cttctgttct gagatggggg tggtgggcag 120
tateteatet ttgggtteea caatgeteac gtggteagge aggggettet tagggeeaat 180
cttaccagtt gggtcccagg gcagcatgat cttcaccttg atgcccagca caccctgtct 240
gagcaacacg tggcgcacag caagtgtcaa cgtaagtaag ttaacagggt ctccgctgtg 300
gatcatcagg ccatccacaa acttcatgga tttaaccctc tgtcctcgga g
<210> 301
<211> 330
<212> DNA
<213> Homo sapiens
<400> 301
tegageggee geeegggeag gtgttteaga ggtteeaagg teeactgtgg aggteeeagg 60
agtgctggtg gtgggcacag aggtccgatg ggtgaaacca ttgacataga gactgttcct 120
gtccagggtg taggggccca gctctttgat gccattggcc agttggctca gctcccagta 180
cagccgctct ctgttgagtc cagggctttt ggggtcaaga tgatggatgc agatggcatc 240
cactccagtg gctgctccat ccttctcgga cctgagagag gtcagtctgc agccagagta 300
cagagggcca acactggtgt tctttgaata
                                                                   330
```

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<210> 302·
<211> 317
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 129, 295
<223> n = A, T, C or G
agcgtggtcg cggccgaggt ctgtactggg agctaagcaa actgaccaat gacattgaag 60
agetgggeee ctacaecetg gacaggaaca gtetetatgt caatggttte acceateaga 120
getetgtgne caccaccage acteetggga cetecacagt ggattteaga aceteaggga 180
ctccatcctc cetetecage cecacaatta tggetgetgg ecetetectg gtaccattea 240
ccctcaactt caccatcacc aacctgcagt atggggagga catgggtcac cctgnctcca 300
ggaagttcaa caccaca.
                                                                     317
<210> 303
<211> 283
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 139, 146, 195
<223> n = A, T, C or G
<400> 303
tcgagcggcc gcccggacag gtctgggcgg atagcaccgg gcatattttg gaatggatga 60
ggtctggcac cctgagcagt ccagcgagga cttggtctta gttgagcaat ttggctagga 120
ggatagtatg cagcacggnt ctgagnctgt gggatagctg ccatgaagta acctgaagga 180
ggtgctggct ggtangggtt gattacaggg ttgggaacag ctcgtacact tgccattctc 240
tgcatatact ggttagtgag gtgagcctgg ccctcttctt ttg
<210> 304
<211> 72
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 59
<223> n = A, T, C \text{ or } G
<400> 304
agcgtggtcg cggccgaggt gagccacagg tgaccggggc tgaagctggg gctgctggnc 60
ctgctggtcc tg
<210> 305
<211> 245
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 5, 1\overline{1}, 22, 98, 102
```

```
<223> n = A, T, C or G
<400> 305
cagengetee naeggggeet gngggaccaa caacacegtt tteaccetta ggeeetttgg 60
ctcctctttc tcctttagca ccaggttgac cagcagcncc ancaggacca gcaaatccat 120
tggggccagc aggaccgacc tcaccacgtt caccagggct tccccgagga ccagcaggac 180
cagcaggace ageagececa gettegeece ggteacetgt ggeteacete ggeegegace 240
acgct
<210> 306
<211> 246
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 144, 159
<223> n = A, T, C or G
<400> 306
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atccagaacg agaaggagac catgcaaagc ctgaacgacc gcctggcctc ttacctggac 120
agagtgagga gcctggagac cganaaccgg aggctggana gcaaaatccg ggagcacttg 180
gagaagaagg gaccccaggt caagagactg gagccattac ttcaagatca tcgagggacc 240
tggagg
<210> 307
<211> 333
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 5
<223> n = A, T, C or G
<400> 307
aggranging eggeogaggi coagcietgi cicatactig actitaaagi catcageage 60
aagacgggca ttgtcaatct gcagaacgat gcgggcattg tccgcagtat ttgcgaagat 120
ctgagccctc aggtcctcga tgatcttgaa gtaatggctc cagtctctga cctggggtcc 180
cttettetee aagtgeteee ggattttget etceageete eggttetegg tetecagget 240
cctcactctg tccaggtaag aaggcccagg cggtcgttca ggctttgcat ggtctccttc 300
tcgttctgga tgcctcccat tcctgccaga ccc
                                                                   333
<210> 308
<211> 310
<212> DNA
<213> Homo sapiens
<400> 308
tegageggee geeegggeag gteaggaage acattggtet tagageeact geeteetgga 60
ttccacctgt gctgcggaca tctccaggga gtgcagaagg gaagcaggtc aaactgctca 120
gatcagtcag actggctgtt ctcagttctc acctgagcaa ggtcagtctg cagccagagt 180
acagagggcc aacactggtg ttcttgaaca agggcttgag cagaccctgc agaaccctct 240
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ttggtgatgg
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<210> 309

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<211> 429
<212> DNA
<213> Homo sapiens
<400> 309
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gctgatgtac cagttcttct gggccacact gggctgagtg gggtacaccg caggtctcac 180
cagtetecat gttgcagaag actttgatgg catecaggtt gcageettgg ttggggtcaa 240
tecagtacte tecaetette cagteagaag tgggeacate ttgaggteae eggeaggtge 300
egggeegggg gttettgegg ettgeeetet gggeteegga tgttetegat etgettgget 360
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cccgctcga
<210> 310
<211> 430
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 342
<223> n = A,T,C or G
<400> 310
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egeacetgee gtgaceteaa gatgtgecae tetgactgga agagtggaga gtactggatt 180
gaccccaacc aaggctgcaa cctggatgcc atcaaagtct tctgcaacat ggagactggt 240
gagacetgeg tgtaceceae teageceagt gtgggeeeag aagaaaetgg tacateagea 300
aggaacccca aggacaagag gcattgtctt ggttcggcga gnagcatgac ccgatggatt 360
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gaccaccgct
<210> 311
<211> 2996
<212> DNA
<213> Homo sapiens
<400> 311
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acagagagca getgtatttg gagetgagee agetgaeeea cageateaet gagetgggee 120
cctacaccct ggacagggac agtctctatg tcaatggttt cacacagegg agctctgtgc 180
ccaccactag cattcctggg acccccacag tggacctggg aacatctggg actccaqttt 240
ctaaacctgg tecetegget gecageeete teetggtget atteactete aactteacca 300
tcaccaacct gcggtatgag gagaacatge agcaccctgg ctccaggaag ttcaacacca 360
cggagagggt cettcaggge ctggtecetg ttcaagagea ccagtgttgg ccetctgtac 420
tetggetgea gaetgaettt geteaggeet gaaaaggatg ggaeageeae tggagtggat 480
gecatetgea eccaecaece tgaececaaa agecetagge tggacagaga geagetgtat 540
tgggagctga gccagctgac ccacaatatc actgagctgg gcccctatgc cctggacaac 600
gacageetet tigicaaigg titeaeteai eggageteig igiceaecae eageaeteet 660
gggacccca cagtgtatet gggagcatet aagactecag cetegatatt tggecettea 720
gctgccagcc atctcctgat actattcacc ctcaacttca ccatcactaa cctgcggtat 780
gaggagaaca tgtggcctgg ctccaggaag ttcaacacta cagagagggt ccttcagggc 840
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<210> 312

<211> 914

<212> PRT

<213> Homo sapiens

<400> 312

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His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Pro Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp

Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln

<210> 313

<211> 656

<212> DNA

<213> Homo sapiens

<400> 313

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<211> 519
<212> DNA
<213> Homo sapiens
<400> 314
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gtttaaggat ggtctcggtg gttaggccca ctagaataaa ctgagtccaa tacctctaca 180
cagttatgtt taactgggct ctctgacacc gggaggaagg tggcggggtt taggtgttgc 240
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cattcattag ctaatggtgt cctttggtat ttattaaaat caccacagca tagggggact 360
ttatgtttag gttttgtcta agagttagct tatctgcttc ttgtgctaac agggctattg 420
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gataggccac tggccttgga cctcggccgc gaccacqct
<210> 315
<211> 441
<212> DNA
<213> Homo sapiens
<400> 315
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ttqtcaaacq tctctqcact qttttcaqcc tctccacqtt qcctctgtcc tqcttcttaq 240
ttccttcttt gtgacaaacc aaaagaataa gaggatttag aacaggactg cttttcccct 300
atgatttaaa aattccaatg actttcgccc ttgggagaaa tttccaagga aatctctctc 360
getegetete teegttttee tttgtgaget tetgggggag ggttagtggt gaetttttga 420
tacgaaaaaa tgcattttgt g
<210> 316
<211> 247
<212> DNA
<213> Homo sapiens
<400> 316
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ccagtctage ttggtaagaa gagagacatg cccccaacct cggcgccctt tttcctcacg 180
atctgctgtc cttacttcag cgactgcagg agcttcacct gcaagaaaac agcattgagc 240
                                                                   247
·tgctqac
<210> 317
<211> 409
<212> DNA
<213> Homo sapiens
<400> 317
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cacqatqtqq gatqaacagc agccttggtt tgtagcccaq ggtgtccatq gatttgaccc 120
gaatgctccc tggaggccct gtggcgagga caggcactgg atggtccaga ccctctggct 180
ggaggagtgg tggagccagg actgggcctt cagccatgag ggctagaata acctgacctc 240
ttgcattcta acactgggtc attaatgaca cctttccagt ggatgttgca aaaaccaaca 300
ctgtcaggaa cctggccctg ggagggctca ggtgagctca caaggagagg tcaagccaag 360
ccaaagggta ggkaacacac aacaccaggg gaaaccagcc cccaaacca
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<210> 318
<211> 320
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 6, 1\overline{7}, 24, 271
<223> n = A, T, C or G
<400> 318
caaggnagat cttaagnggg gtcntatgta agtgtgctcc tggctccagg gttcctggag 60
cctcacqaqq tcaqqqqaac ccttqtaqaa ctccaccagc agcatcatct cgtgaaggat 120
qtcattqqtc aqqaaqctqt cctqqacqta qqccatctcc acatccatqq ggatqccata 180
qtcactqqqc ctttqctcqq qaqqaqqcat cacccaqaaa qqcqaqatct tqqactcqqq 240
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gctggagccc tgcagccgca
<210> 319
<211> 212
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 172 ,
<223> n = A, T, C or G
<400> 319
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agggggtcct tccctggctc aggcagatgg gaagatgagg aagccgctga agacgctgtc 120
ggcctcagag ccctggtaaa tgtgaccctt tttggggtct ttttcaaccc anacctggtc 180
accetgetge agacetegge egegaceaeg et
<210> 320
<211> 769
<212> DNA
<213> Homo sapiens
<400> 320
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tggagggegt ettteteeat cagegeatae tgageagggg tacteagate ettettggaa 180
cctacaagga agagaagcac actggaaggg tcattctcct tcagggcatc ggccagccac 240
tgcctgccat gggaggtgga aagtaaggga tgagtgagtc tgcagggccc ctcccactga 300
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gccccttacc ttgagctcct ctatagtagg ttgatgcaat gcatttgaac ctctcctgcc 660
cagcggtatc ccaactggaa ggaaggaaga gtgaagcaca ggtatgtatc ttggggggtg 720
tgggtgctgg ggagaaggga tagctggaag gggtgtggaa gcactcaca
<210> 321
<211> 690
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> 633, 666
<223> n = A, T, C or G
<400> 321
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cctactcccc cggaggcaac tgggaggtca acgggaagac aatcatcccc tataagaaqq 120
gtgcctggtg ttcgctctgc acagccagtg tctcaggctg cttcaaagcc tgggaccatg 180
caggggggct ctgtgaggtc cccaggaatc cttgtcgcat gagctgccag aaccatggac 240
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aagtgaggtg cagcctgcag tgtgtgcacg gccggttccg ggaggaggag tgctcgtgcg 360
tetgtgacat eggetaeggg ggageecagt gtgeeaceaa ggtgeatttt eeetteeaca 420
cetgtgacet gaggategae ggagaetget teatggtgte tteagaggea gacacetatt 480
acagaagcca ggatgaaatg tcagaggaat ggcggggtgc tggcccagat caagagccag 540
aaagtgcagg acatcetege ettetatetg ggeegeetgg agaccaecaa egaggtgaet 600
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teettneget gggeeacagg ggageaceag
<210> 322
<211> 104
<212> DNA
<213> Homo sapiens
<400> 322
gtegcaagec ggageaceae catgtageet tteeegaagt aceggaeett etecteetee 60
acgctcacat cacggacatc atggagcagg accaccacct ggtc
                                                                   104
<210> 323
<211> 118
<212> DNA
<213> Homo sapiens
<400> 323
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actagtgaat gaagaacgaa cactggaagt agaaatagag cctggggtga gagacgga
<210> 324
<211> 354
<212> DNA
<213> Homo sapiens
<400> 324
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agcggtctgt. atggacccag gcttgtcaaa ctgtactata cacatcgtga cagtcaccat 120
taacggagat gatgccgaaa acgcaaggcc gaagccaaag ccaggggatg gagagtttgt 180
ggaagtcatt tctttaccca agaatgacct gctgcagaga cttgatgctc tggtagetga 240
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<210> 325
<211> 642
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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<222> 1
<223> n = A, T, C or G
<400> 325
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ggcacttcaa taggtcgctg attggtcctt gcaccagcag tggtagtcgt acctatttca 180
gagaggtctg aaattcaggt tcttagtttg ccagggacag gccctacctt atatttttt 240
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gagttatctg ggtggtctct agccatctgg gcagtgtggt tctgtctaac caaagggcat 360
tggcctcaaa ccctgcattt ggtttagggg ctaacagagc tcctcagata atcttcacac 420
acatgtaact gctggagatc ttattctatt atgaataaga aacgagaagt ttttccaaag 480
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cccattcaga ctttgccaga gtcaagccaa ggattgcttt tttgctacag ttttctgcca 600
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                                                                   642
<210> 326
<211> 455
<212> DNA
<213> Homo sapiens
<400> 326
tecqtqagqa tgagettega gteetteace aggeactgea ggggcacagt cacgteaate 60
accttcacct totogetott cotgetottg toattgacaa acttcccgta ccaggcattg 120
acquitquique qqcccattct qqactcttct qcctcaatta tccttcggac agattcctgc 180
atcageegga cageggaete egeetettge ttettetgea geacateggt ggeggegett 240
tecetetget tetecaatte ettetette tgageeetga ggtatggttt gatgateaga 300
cggtgcatgg caaagtagac cactagaggc cccacggtgg catagaacat ggcgctgggc 360
agaagctggt ccgtcaagtg aatagggaag aagtatgtct gactggccct gttgagcttg 420
actttgagag aaacgccctg tggaactcca acgct
                                                                   455
<210> 327
<211> 321
<212> DNA
<213> Homo sapiens
<400> 327
ttcactgtqa actcgcagtc ctcgatgaac tcgcacagat gtgacagccc tgtctccttg 60
ctctctgagt tctcttcaat gatgctgatg atgcagtcca cgatagcgcg cttatactca 120
aagccaccet etteeegeag catggtgaac aggaagttea taaggaegge gtgtttgega 180
ggatatttet gacacaggge actgatggee tggacaacca ceacettgaa tteateegag 240
atttctgaca tgaaggagga gatctgcttc atgaggcggt cgatgctgct ctcgctgccc 300
gtcttaagga gggtggtgat g
<210> 328
<211> 476
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 302, 311
<223> n = A, T, C or G
<400> 328
tgcaggaggg gccatggggg ctgtgaatgg gatgcagccc catggtgtcc ctgataaatc 60
cagtgtgcag tctgatgaag tctgggtggg tgtggtctac gggctggcag ctaccatgat 120
ccaagaggta atgcactcct tttcccatct ctccaccatc tgtatcctgg ccmagaaaaa 180
```

```
cttcccttca aaccaaccaa aatttccttt caaaggcata acccaaatgc catccttggt 240
coggtetaat aaagceteec ceattittee cetggtatge atteceagge teeetggeet 300
threagggett netgtetgtg ggteatagtt tateteetee eacttgetgg gageteettg 360
aaggcaaaga ctctactgcc tccatctatc cagtggaagt ggctcttcag agggtgccaa 420
gttagtatgt atgactgtca tctctcccaa cagggcctga cttggsaggg cttcca
<210> 329
<211> 340
<212> DNA
<213> Homo sapiens
<400> 329
cgagggagat tgccagcacc ctgatggaga gtgagatgat ggagatcttg tcagtgctag 60
ctaagggtga ccacagccct gtcacaaggg ctgctgcagc ctgcctggac aaagcagtgg 120
aatatgggct tatccaaccc aaccaagatg gagagtgagg gggttgtccc tgggcccaag 180
geteatgeac acgetaceta ttgtggcacg gagagtaagg acggaagcag etttggctgg 240
tggtggctgg catgcccaat actettgccc atectcgctt gctgccctag gatgtcctct 300
gttctgagtc agcggccacg ttcagtcaca cagccctgct
<210> 330
<211> 277
<212> DNA
<213> Homo sapiens
<400> 330
tgtcaccatc acattggtgc caaataccca gaagacatcg tagatgaaga gtccgcccag 60
caggatgcag ccagtgctga cattgttgag gtgcaggagc tctactccat taagggagaa 120
ggccaggcca aaaaggttgt tggcaatcca qtqcttcctc aqcagqtacc aqacqccaac 180
gatgetgete aggeceagge acaccaggte ettggtgtea aatteataat tgatgatete 240
ctccttgttt tcccagaacc ctgtgtgaag agcagac
<210> 331
<211> 136
<212> DNA
<213> Homo sapiens
<400> 331
ttgcttccca cctcctttct ctgtcctctc ctgaggttct gccttacaat ggggacactg 60
atacaaacca cacacaat gaggatgaaa acagataaca ggtaaaatga cctcacctgc 120
ccgggcggcc gctcga
                                                                   136
<210> 332
<211> 184
<212> DNA
<213> Homo sapiens
<400> 332
ttgtgagata aacgcagata ctgcaatgca ttaaaacgct tgaaatactc atcagggatg 60
ttgctgatct tattgttgtc taagtagaga gttagaagag agacagggag accagaaggc 120
agtotggota totgattgaa gotcaagtoa aggtattoga gtgatttaag acotttaaaa 180
gcag
<210> 333
<211> 384
<212> DNA
<213> Homo sapiens
<400> 333
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cggaaaactt cgaggaattg ctcaaagtgc tgggggtgaa tgtgatgctg aggaagattg 60
ctgtggctgc agcgtccaag ccagcagtgg agatcaaaca ggagggagac actttctaca 120
tcaaaacctc caccaccgtg cgcaccacag agattaactt caaggttggg gaggagtttg 180
aggagcagac tgtggatggg aggccctgta agagcctggt gaaatgggag agtgagaata 240
aaatggtctg tgagcagaag ctcctgaagg gagagggccc caagacctcg tggaccagag 300
aactgaccaa cgatggggaa ctgatcctga ccatgacggc ggatgacgtt gtgtgcacca 360
gggtctacgt ccgagagtga gcgg
<210> 334
<211> 169
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 2, 165
<223> n = A, T, C or G
<400> 334
cnacaaacag agcagacacc ctggatccgg tcctgctact ggccaggacg gctggaccgt 60
aaaattgaat ttccacttcc tgaccgccgc cagaagagat tgattttctc cactatcact 120
agcaagatga acctctctga ggaggttgac ttggaagact atgtngccc
<210> 335
<211> 185
<212> DNA
<213> Homo sapiens
<400> 335
ccaggtttgc agcccaggct gcacatcagg ggactgcctc gcaatacttc atgctgttgc 60
tgctgactga tggtgctgtg acggatgtgg aagccacacg tgaggctgtg gtgcgtgcct 120
cgaacctgcc catgtcagtg atcattgtgg gtgtgggtgg tgctgacttt gaggccatgg 180
agcag
<210> 336
<211> 358
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 26
<223> n = A, T, C or G
<400> 336
ctgcccctgc cttacggcgg ccaganacac acccaggatg gcattggccc caaacttgga 60
tttgttetca gteccateca actecageat caggttgtec agtttetett getecaceae 120
agagagacct gagctgatga gggctggcgo gatggtggag ttgatgtggt ccactgcctt 180
caggacacct ttgcctaagt aacgctgttt gtctccatcc ctcagctcca gggcctcata 240
gatgecegta gaggeteeae tgggeaetge ageceggaaa agacetttgg eagtatagag 300
atccacctcc actgtggggt tcccgcggga gtccaggatc tcccgggccc agatcttc
<210> 337
<211> 271
<212> DNA
<213> Homo sapiens
<220>
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```
<221> misc_feature
<222> 17
<223> n = A, T, C or G
<400> 337
cacaaagcca ccagconggg aaatcagaat ttacttgatg caactgactt gtaatagcca 60
gaaatcctgc ccagcatggg attcagaacc tggtctgcaa ccaaatccac cgtcaaagtt 120
catacaggat aaaacaaatt caattgcctt ttccacatta atagcatcaa gcttccccaa 180
caaagccaaa gttgccaccg cacaaaaaga gaatcttgtg tcaatttctc cctactttat 240
aaaagtagat ttttcacatc ccatgaagca g
<210> 338
<211> 326
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 15, 17, 18
<223> n = A, T, C or G
<400> 338
ctgtgctccc gactngnnca tctcaggtac caccgactgc actgggcggg gccctctggg 60
gggaaagget ceaeggggea gggatacate tegaggeeag teateetetg gaggeageec 120
aatcaggtca aagattttgc ccaactggtc ggcttcagag tttccacaga agagaggctt 180
tegaegaaac atetetgeaa agatacagee aacaeteeac atgteeacag gtgttgeata 240
tgtggactgc agaagaactt cgggagctcg gtaccagagt gtaacaacca cgggtgtaag 300
tgccatctgg tagctgtaga ttctgg
                                                                    326
<210> 339
<211> 260
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 47, \overline{5}4, 60, 69, 90, 91, 96, 113, 117, 119, 195
<223> n = A, T, C or G
<400> 339
ttcacctgag gactcatttc gtgccctttg ttgacttcaa gcaaagncct tcangqtctn 60
caaggacgnc acatttccac ttgcgaatgn netcangget catettgaag aanaagnane 120
ccaagtgctg gatcccagac tcgggggtaa ccttgtgggt aagagctcat ccagtttatg 180
ctttaggacg tccanctact cgggggagct ggaagcctgc gtggatgcgg ccctgctgga 240
cctcggccgc gaccacgcta
<210> 340
<211> 220
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 15, 18
<223> n = A, T, C or G
<400> 340
ctggaagece ggctnggnet ggcageggaa ggagecagge aggtteaege ageggtgetg 60
```

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geagtagegg tageggeact egtetatgte cacacacteg ggeeegatet tgeqqtaace 120
atcagggcag gtgcactgat aggagccagg caagttatgg cagtcctggc tggggcgaca 180
gtcgtgcagg gcctgggcac actcgtccac atccacacag
<210> 341
<211> 384
<212> DNA
<213> Homo sapiens
<400> 341
ctgctaccag gggagcgaga gctgactatc ccagcctcgg ctaatgtatt ctacgccatg 60
gatggagett cacacgattt ceteetgegg cageggegaa ggteetetae tgetacaceg 120
ggcgtcacca gtggcccgtc tgcctcagga actcctccga gtgagggagg agggggctcc 180
tttcccagga tcaaggccac agggaggaag attgcacggg cactgttctg aggaggaagc 240
cccgttggct tacagaagtc atggtgttca taccagatgt gggtagccat cctqaatggt 300
ggcaattata tcacattgag acagaaattc agaaagggag ccagccaccc tggggcagtg 360
aagtgccact ggtttaccag acag
                                                                   384
<210> 342
<211> 245
<212> DNA
<213> Homo sapiens
<400> 342
ctggctaagc tcatcattgt tactggtggg caccatgtcc ttgaagcttc aggcaagcaa 60
tgtaaccaac aagaatgacc ccaagtccat caactctcga gtcttcattg gaaacctcaa 120
cacagetetg gtgaagaaat cagatgtgga gaceatette tetaagtatg geegtgtgge 180
eggetgttet gtgcacaagg getatgeett tgtteagtae tecaatgage gecatgeeg 240
ggcag
<210> 343
<211> 611
<212> DNA
<213> Homo sapiens
<400> 343
ccaaaaaaaat caagatttaa tttttttatt tgcactgaaa aactaatcat aactgttaat 60
teteagecat etttgaaget tgaaagaaga gtetttggta ttttgtaaae gttageagae 120
tttcctgcca gtgtcagaaa atcctattta tgaatcctgt cggtattcct tggtatctga 180
aaaaaatacc aaatagtacc atacatgagt tatttctaag tttgaaaaat aaaaagaaat 240
tgcatcacac taattacaaa atacaagttc tggaaaaaat atttttcttc attttaaaac 300
tttttttaac taataatggc tttgaaagaa gaggcttaat ttgggggtgg taactaaaat 360
caaaagaaat gattgacttg agggtctctg tttggtaaga atacatcatt agcttaaata 420
agcagcagaa ggttagtttt aattatgtag cttctgttaa tattaagtgt tttttgtctq 480
ttttacctca atttgaacag ataagtttgc ctgcatgctg gacatgcctc agaaccatga 540
atagcccgta ctagatcttg ggaacatgga tcttagagtc ctttggaata agttcttata 600
taaatacccc c
<210> 344
<211> 311
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 1, 275, 284, 296, 297, 300
<223> n = A, T, C or G
```

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<400> 344
nctcgaaaaa gcccaagaca gcagaagcag acacctccag tgaactagca aagaaaagca 60
aagaagtatt cagaaaagag atgtcccagt tcatcgtcca gtgcctgaac ccttaccgga 120
aacctgactg caaagtggga agaattacca caactgaaga ctttaaacat ctggctcgca 180
agctgactca cggtgttatg aataaggagc tgaagtactg taagaatcct gaggacctgg 240
agtqcaatga qaatgtgaaa cacaaaacca aggantacat taanaagtac atgcannaan 300
tttggggctt g
<210> 345
<211> 201
<212> DNA
<213> Homo sapiens
<400> 345
cacacggtca tecegactge caacetggag geecaggeec tgtggaagga geegggeage 60
aatqtcacca tqaqtqtqqa tqctqaqtqt qtqcccatqq tcaqqqacct tctcaqqtac 120
ttctactccc gaaggattga catcaccctg tcgtcagtca agtgcttcca caagctggcc 180
tctgcctatg gggccaggca g
<210> 346
<211> 370
<212> DNA
<213> Homo sapiens
<400> 346
etgetecagg gegtggtgtg cettegtgge etetgeetee teegaggage eaggetgtgt 60
tctcttcaga atgttctgga gcagcagttt gaggcgggtg atgcgttgga agggcagaat 120
caqaaaqqac ttqaqggaaa qqcqctggca gacggggtcg ctctccagct tctccaaqac 180
ctcccggaaa ttgctgttgc tattcatcag gctctggaag gtgcgttcct gataggtctg 240
gttggtgaca taaggcaggt agacccggcg gaagtctggg gcgtggttca ggactacgtc 300
acatacttgg aaggagaaga tattgttctc aaagttctct tccaggtctg aaaggaacgt 360
ggcgctgacg
<210> 347
<211> 416
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 416
<223> n = A, T, C or G
<400> 347
ctgttgtgct gtgtatggac gtgggcttta ccatgagtaa ctccattcct ggtatagaat 60
ccccatttga acaagcaaag aaggtgataa ccatgtttgt acagcgacag gtgtttgctg 120
agaacaagga tgagattgct ttagtcctgt ttggtacaga tggcactgac aatccccttt 180
ctqqtqqqqa tcaqtatcaq aacatcacaq tqcacaqaca tctqatqcta ccaqattttq 240
atttgctgga ggacattgaa agcaaaatcc aaccaggttc tcaacaggct gacttcctgg 300
atgcactaat cgtgagcatg gatgtgattc aacatgaaac aataggaaag aagtttggag 360
aaqaqqcata ttqaaatatt cactqacctc aagcagcccg attcagcaaa agtcan
<210> 348
<211> 351
<212> DNA
<213> Homo sapiens
<400> 348
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```
gtacaggaga ggatggcagg tgcagagcgg gcactgagct ctgcaggtga aagggctcgg 60
cagttqqatq ctctcctqqa qqctctqaaa ttqaaacqqq cagqaaataq tctqqcagcc 120
tetacageag aagaaaegge aggeagtgee eagggaegag eaggagaeag atgeetteet 180
cttgtctcaa ctgcaaagag gcgttccttc ctctttcact aatcctcctc agcacagacc 240
ctttacgggt gtcaggctgg gggacagtaa ggtctttccc ttcccacaag gccatatctc 300
aggetgtete agtgggggga aacettggae aataceeggg etttettggg e
<210> 349
<211> 207
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 1
<223> n = A, T, C or G
<400> 349
neegggacat etecaceete aacagtggca agaagageet ggagaetgaa cacaaggeet 60
tgaccagtga gattgcactg ctgcagtcca qqctgaagac agagggctct gatctgtgcg 120
acagagtgag cgaaatgcag aagctggatg cacaggtcaa ggagctggtg ctgaagtcgg 180
cggtggaggc tgagcgcctg gtggctg
<210> 350
<211> 323
<212> DNA
<213> Homo sapiens
<400> 350
ccatacaggg ctgttgccca ggccctagag gtcattcctc gtaccctgat ccagaactgt 60
qqqqccaqca ccatccqtct acttacctcc cttcqqqcca aqcacaccca qqaqaactqt 120
gagacctggg gtgtaaatgg tgagacgggt actttggtgg acatgaagga actgggcata 180
tgggagccat tggctgtgaa gctgcagact tataagacag cagtggagac ggcagttctg 240
ctactgcgaa ttgatgacat cgtttcaggc cacgaaaaga aaggcgatga ccagagccgg 300
caaggegggg ctcctgatge tgg
<210> 351
<211> 353
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
\langle 222 \rangle 12, \overline{2}5, 39, 42
<223> n = A, T, C \text{ or } G
<400> 351
equegeated entgqteest tecanteest titeettint engggaacqt gtatgeqqtt 60
tgtttttgtt ttgtagggtt tttttccttc tccacctctc cctgtctctt ttgctccatg 120
ttgtccgttt ctgtggggtt aggtttatgt ttttaatcat ctgaggtcac gtctatttcc 180
teeggacteg cetgettggt ggegattete caceggttaa tatggtgegt ceettttte 240
ttttgttgcq aatctgagcc ttcttcctcc agcttctgcc ttttgaactt tgttcttcgg 300
ttctgaaacc atacttttac ctgagtttcc gtgaggctga ggctgtgtgc caa
<210> 352
<211> 467
<212> DNA
<213> Homo sapiens
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<400> 352
ctgcccacac tgatcacttg cgagatgtcc ttagggtaca agaacaggaa ttgaagtctg 60
aatttgagca gaacctgtct gagaaactct ctgaacaaga attacaattt cgtcgtctca 120
qtcaagaqca agttqacaac tttactctqq atataaatac tgcctatgcc agactcagag 180
gaatcgaaca ggctgttcag agccatgcag ttgctgaaga ggaagccaga aaagcccacc 240
aactctggct ttcagtggag gcattaaagt acagcatgaa gacctcatct gcagaaacac 300
ctactatece getgggtagt geagttgagg ceateaaage caactgttet gataatgaat 360
tcacccaagc tttaaccgca gctatccctc cagagtccct gacccgtggg gtgtacagtg 420
aggagacct tagagecegt ttetatgetg tteaaaaact ggeeega
<210> 353
<211> 350
<212> DNA
<213> Homo sapiens
<400> 353
etgetgeage caeagtagtt ceteceatgg tgggtggeee teetggteet getggeeeag 60
gaaatctgtc cccaccagga acagcccctg gaaaacggcc ccgtcctcta ccaccttgtg 120
gaaatgctgc acgggaactg cctcctggag gaccagcttt accttcccca gacatttgtc 180
ctgattgtgt agttttcctg gactgcattt caaattgact caggaactgt ttattgcatg 240
gagttacaac aggattctga ccatgaagtt ctcttttagg taacagatcc attaactttt 300
ttgaagatgc ttcagatcca acaccaacaa gggcaaaccc ctttgactgg
                                                                   350
<210> 354
<211> 351
<212> DNA
<213> Homo sapiens
<400> 354
atttagatga gatctgaggc atggagacat ggagacagta tacagactcc tagatttaag 60
ttttaggttt tttgcttttc taatcaccaa ttcttatata caatgtatat tttagactcg 120
agcagatgat catcttcatc ttaagtcatt ccttttgact gagtatggca ggattagagg 180
gaatggcagt atagatcaat gtctttttct gtaaagtata ggaaaaacca gagaggaaaa 240
aaagagetga caattggaag gtagtagaaa attgacgata atttettett aacaaataat 300
agttgtatat acaaggaggc tagtcaacca gattttattt gttgagggcg a
<210> 355
<211> 308
<212> DNA
<213> Homo sapiens
<400> 355
ttttqqcqca aqttttacaq attttattaa aqtcqaaqct attqqtcttq qaaqatgaaa 60
atgcaaatgt tgatgaggtg gaattgaagc cagatacctt aataaaatta tatcttggtt 120
ataaaaataa gaaattaagg gttaacatca atgtgccaat gaaaaccgaa cagaagcagg 180
aacaagaaac cacacacaaa aacategagg aagacegcaa actaetgatt caggeggeca 240
tegtgagaat catgaagatg aggaaggtte tgaaacacca geagttaett ggegaggtee 300
tcactcag
<210> 356
<211> 207
<212> DNA
<213> Homo sapiens
<400> 356
ctgtcccaag tgctcccaga aggcaggatt ctgaagacca ctccagcgat atgttcaact 60
atgaagaata ctgcaccgcc aacgcagtca ctgggccttg ccgtgcatcc ttcccacgct 120
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ggtactttga cgtggagagg aactcctgca ataacttcat ctatggaggc tgccggggca 180
ataagaacag ctaccgctct gaggagg
<210> 357
<211> 188
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222>25, \overline{29}
<223> n = A, T, C \text{ or } G
<400> 357
tegaceaege cetegtageg catgngetne aggacgatge teagagtgat gaacaeeeeg 60
gtgcggccca cgccagcact gcagtgcacc gtgataggcc catcctgtcc aaactgctcc 120
ttggtcttat gcacctgccc gatgaagtca atgaatccct cgcctgtctt gggcacgccc 180
tgctctgg
<210> 358
<211> 291
<212> DNA
<213> Homo sapiens
<400> 358
ctgggagcat cggcaagcta ctgccttaaa atccgatctc cccgagtgca caatttctgt 60
cccttttaag gqttcacaac actaaagatt tcacatgaaa gggttgtgat tgatttgagc 120
aggcaggcgg tacgtgacag gggctgcatg caccggtggt cagagagaaa cagaacaggg 180
cagggaattt cacaatgttc ttctatacaa tggctggaat ctatgaataa catcagtttc 240
taagttatgg gttgatttt aactactggg tttaggccag gcaggcccag g
<210> 359
<211> 117
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
\langle 222 \rangle 79, \overline{98}, 100
<223> n = A, T, C or G
<400> 359
gccaccacac tccagcctgg gcaatacagc aagactgtct caaaaaaaaa aaaaaaaaa 60
cccaaaaaa ctcaaaaang taatgaatga tacccaangn gccttttcta gaaaaag
<210> 360
<211> 394
<212> DNA
<213> Homo sapiens
<400> 360
ctgttcctct ggggtggtcc agttctagag tgggagaaag ggagtcaggc gcattgggaa 60
tcqtqgttcc agtctggttg cagaatctgc acatttgcca agaaattttc cctgtttgga 120
aagtttgeec cagettteec gggeacaeca cettttgtee caagtgtetg ceggtegaec 180
aatotgootg coacacattg accaagooag accoggttoa cocagotoga ggatocoagg 240
ttgaagagtg gccccttgag gccctggaaa gaccaatcac tggacttctt cccttgagag 300
teagaggtea ecceptgatte tqcetgcace ttatcattga tetgcagtga tttetgcaaa 360
tcaagagaaa ctctgcaggg cactcccctg tttc
                                                                     394
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<210> 361
<211> 394
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 28, 31
<223> n = A,T,C or G
<400> 361
ctgggcggat agcaccgggc atattttntt natggatgag gtctggcacc ctgagcagtc 60
cagcgaggac ttggtcttag ttgagcaatt tggctaggag gatagtatgc agcacggttc 120
tgagtctgtg ggatagctgc catgaagtaa cctgaaggag gtgctggctg gtaggggttg 180
attacagggt tgggaacagc tcgtacactt gccattctct gcatatactg gttagtgagg 240
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<212> DNA
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acagttatgt ttaactgggc tctctgacac cgggaggaag gtggcggggt ttaggtgttg 240
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<210> 363
<211> 323
<212> DNA
<213> Homo sapiens
<400> 363
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<210> 364
<211> 393
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 29
<223> n = A,T,C or G
<400> 364
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<212> DNA
<213> Homo sapiens
<400> 365
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<213> Homo sapiens
<400> 366
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<210> 367
<211> 327
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 34, 54, 55
<223> n = A, T, C or G
<400> 367
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tgatettgaa gtaatggete eagtetetga eetggggtee ettettetee aagtgeteee 180
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<210> 368
<211> 306
<212> DNA
<213> Homo sapiens
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<220>

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cctgtgaacc aagtgtttgg gcaggatgag atgatcgacg tcatcggggt gaccaagggc 240
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cgagga
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<211> 394
<212> DNA
<213> Homo sapiens
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<211> 653
<212> DNA
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ctggtgtcac agaggctact attactggcc tggaaccggg aaccgaatat acaatttatg 180
tcattgccct gaagaataat cagaagagcg agcccctgat tggaaggaaa aagacagacg 240
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ttccttccac agttcaaaag acccctttcg tcacccaccc tgggtatgac actggaaatg 360
gtattcagct tcctggcact tctggtcagc aacccagtgt tgggcaacaa atgatctttg 420
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 <210> 371
 <211> 268
 <212> DNA
 <213> Homo sapiens
 <400> 371
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 gctccacctg gactacatcg ggccttgcaa atacatcccc ccttgcctgg actctgagct 180
 gaccgaatte eccetgegea tgegggactg getcaagaac gteetggtea ecctgtatga 240
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 <210> 372
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<211> 392

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<212> DNA
<213> Homo sapiens
<400> 372
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ggtgctgctg gtactcctgg tctgcaagga atgcctggag aaagaggagg tcttggaagt 180
cctggtccaa agggtgacaa gggtgaacca ggcggtccag gtgctgatgg tgtcccaggg 240
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cctggtgaga gaggtgaaac ctcggccgcg ac
<210> 373
<211> 388
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> 30
<223> n = A, T, C \text{ or } G
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aaccattggc ctgggccagc ttgcacgcct gaagagactc ggtcacggag ccaatctggt 180,
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<210> 374
<211> 393
<212> DNA
<213> Homo sapiens
<400> 374
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gcatcaaggt agacaaggge gtggtccccc tggcagggac aaatggcgag actaccaccc 180
aagggttgga tgggctgtct gagcgctgtg cccagtacaa gaaggacgga gctgacttcg 240
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aaaatgccaa tgttctggcc cgttatgcca gtatctgcca gcagaatggc attgtgccca 360
tcgtggagcc tgagatcctc cctgatgggg acc
<210> 375
<211> 394
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222>30, \bar{3}3
<223> n = A, T, C or G
<400> 375
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aggaaagagg ggatgaactt gcagactctg cgcttgagat cttcaaacaa gcatcagcgt 120
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ggatgaagca ttagcttgaa gcactacagg aggaatgcac cacggcagct ctccgccaat 240
ttctctcaga tttccacaga gactgtttga atgttttcaa aaccaagtat cacactttaa 300
tgtacatggg ccgcaccata atgagatgtg agccttgtgc atgtggggga ggagggagag 360
agatgtactt tttaaatcat gttcccccta aaca
<210> 376
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> 30
<223> n = A, T, C or G
<400> 376
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getecacetg gactacateg ggeettgeaa atacateece cettgeetgg actetgaget 180
gaccgaattc cccctgcgca tgcgggactg gctcaagaac gtcctggtca ccctgtatga 240
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cgagaagaac tataacatgt acatcttccc tg
<210> 377
<211> 292
<212> DNA
<213> Homo sapiens
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ctgccatatg gaggaggete tggagteetg etetgtgtgg tecaggteet ttecaecetg 180
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 <210> 378
 <211> 395
 <212> DNA
 <213> Homo sapiens
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 <211> 223
 <212> DNA
 <213> Homo sapiens .
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<210> 380
<211> 317
<212> DNA
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<210> 381
<211> 392
<212> DNA
<213> Homo sapiens
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<222> 29, 30, 31
<223> n = A, T, C or G
<400> 381
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<211> 234
<212> DNA
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<210> 383
<211> 396
<212> DNA
<213> Homo sapiens
<220>
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<222> 66
<223> n = A, T, C or G
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<211> 396
<212> DNA
<213> Homo sapiens
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128

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Met Pro Glu Val
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Arg Cys Glu Ala
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Ala Ser Gln Val
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Thr Ser Phe Glu
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Ser Val Leu Tyr
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Ile Glu Asn Asp
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Glu Ser Glu Ile
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Leu Met Leu Lys
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Lys Leu Ser
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Cys Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp Ala Ser
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Gln Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn Thr Ser Phe
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Glu
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133

65

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Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile
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Ser Leu Cys Val Ser Ser Phe Phe Ala Ile
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Leu Leu Pro Leu Ser Pro Tyr Leu Met Leu
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Cys Met Ile Glu Asn Asp Ile Ala Lys Ala
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Lys Thr Gly Ala Phe Ser Met Pro Glu Val
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<212> PRT

135

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<210> 433

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Gly Ile Ser Gly Arg His Ser Ile Thr Val
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Phe Glu Pro Asp Ile Lys Leu Ser Asp Ile
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Ile Leu Ala Gly Ala Ile Ala Leu Ile
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<213> Homo sapiens

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                                        75
Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser
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Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro
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                                105
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Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu
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Ser	Gln 370	Leu	Thr	His		Ile 375	Thr	Glu	Leu	Gly	His 380	Tyr	Ala	Leu	Asp
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465			Arg		470					475					480
	_		Arg	485				_	490		<u> </u>	_	-	495	
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		515	Arg				520					525			
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			Glu	565					570					575	
			Ala 580					585					590		
	-	595	Val		_		600					605		_	•
	610		Ala			615					620				
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			Ser	645					650					655	Leu
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	690					695					700				Leu
705				•	710			_		715					Leu 720
				725					730					735	Gly
			740					745					750		Arg
		755					760					765		_	Gln
ъeи	тте	ser	Leu	Arg	rro	GTA	ьys	Asp	етй	чта	ΑΙΆ	inr	етλ	vai	Asp

770 775 780 Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile 790 795 Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln 805 810 Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr 820 825 830 Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His 840 845 Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr 855 860 Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys 865 870 875 Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu 885 890 Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn 900 905 Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn 915 ' 920 925 Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His 935 Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser 945 950 955 Thr Gln His Phe Tyr Pro Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser 970 Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg 980 985 990 Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys 995 1000 1005 Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn 1010 1015 1020 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala 1025 1030 1035 1040 Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr 1045 1050 1055 . Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val 1060 1065 1070 Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn 1080 1085 1075 Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu 1095 1100 Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg 1110 1115 . 1120 Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly 1125 1130 Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 1140 1145

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<213> Homo sapiens

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Lys	Asp	Gly 35		Ala	Thr	Arg	Val 40		Ala	Val	Cys	Thr 45		Arg	Pro
Asp	Pro 50	Lys	Ser	Pro	Gly	Leu 55	Asp	Arg	Glu	Arg	Leu 60	Tyr	Trp	Lys	Leu
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Arg	His	Ser	Leu	Tyr 85	Val	Asn	Gly	Phe	Thr 90	His	Gln	Ser	Ser	Met 95	Thr
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	130			Asn		135					140				
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				Arg 165					170					175	
			180	Arg				185					190		
		195		Asp			200					205			
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			_	Phe 245			_		250					255	
			260	Thr				265					270		
_		275		Ser			280					285			
	290			Thr		295					300				
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				Lys 325					330					335	_
			340	Leu				345					350		
		355		Thr			360					365			-
	370	,		Tyr	•	375					380				
385				Tyr	390					395					400
				Ser 405					410				_	415	
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	450			Tyr		455					460				
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Asn	Thr	Ser	Val	Gly	Pŗo	Leu	Tyr	Ser	Gly	Ser	Arg	Leu	Thr	Leu	Leu

				40E					400					40E	
Δra	Pro	Glu	Lys	485	Glv	Glu	Δ7 a	ሞኮፖ	490	Val	Zen	Δla		495	Thr
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865			Thr		870					875		_			880
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	_	915					920		_			925			
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PCT/US01/22635

148

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 Gly Pro Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val Asn Gly Phe Thr
                                         155
                     150
 His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Pro Thr Val
                 165
                                     170
                                                         175
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Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Pro Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys

Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe 645 650 Cys Leu Val Thr Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys 665 660 670 Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe 680 685 Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr 695 700 Gln Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln 710 715 Pro Thr Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr Ile 725 730 Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn 740 745 750 Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe 760 Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr 775 Phe Arg Ser Val Pro Asn Arg His His Thr Gly Val Asp Ser Leu Cys 795 790 Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu 805 810 Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr 825 820 Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Phe Pro Asn Arg Asn 840 845 835 Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu 855 860 Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly 870 875 Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val 885 890 895 Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp 905 Leu Gln

<210> 479 <211> 1148

<212> PRT

<213> Homo sapiens

<400> 479

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Thr	Thr	Ala 115	Ser	Pro	Leu	Leu	Val 120	Leu	Phe	Thr	Ile	Asn 125	Phe	Thr	Ile
Thr	Asn 130	Leu	Arg	Tyr	Glu	Glu 135	Asn	Met	His	His	Pro 140	Gly	Ser	Arg	ГÀЗ
Phe 145		Thr	Thr	Glu	Arg 150	Val	Leu	Gln	Gly	Leu 155		Arg	Pro	Val	Phe 160
	Asn	Thr	Ser	Val 165		Pro	Leu	Tyr	Ser 170		Суз	Arg	Leu	Thr 175	
Leu	Arg	Pro	Lys 180		Asp	Gly	Ala	Ala 185		Lys	Val	Asp	Ala 190	Ile	Суѕ
Thr	Tyr	Arg 195		Asp	Pro	Lys	Ser 200		Gly	Leu	Asp	Arg 205		Gln	Leu
Tyr	Trp 210		Leu	Ser	Gln	Leu 215		His	Ser	Ile	Thr 220		Leu	Gly	Pro
Tyr 225		Leu	Asp	Arg	Asp 230		Leu	Tyr	Val	Asn 235		Phe	Thr	Gln	Arg 240
	Ser	Val	Pro	Thr 245		Ser	Ile	Pro	Gly 250		Pro	Thr	Val	Asp 255	
Gly	Thr	Ser	Gly 260		Pro	Val	Ser	Lys 265		Gly	Pro	Ser	Ala 270	Ala	Ser
Pro	Leu	Leu 275		Leu	Phe	Thr	Leu 280	_	Phe	Thr	Ile	Thr 285		Leu	Arg
Tyr	Glu 290		Asn	Met	Gln	His 295		Gly	Ser	Arg	Lys 300		Asn	Thr	Thr
Glu 305		Val	Leu	Gln	Gly 310		Leu	Arg	Ser	Leu 315	-	Lys	Ser	Thr	Ser 320
	Gly	Pro	Leu	Tyr 325	Ser	Gly	Cys	Arg	Leu 330		Leu	Leu	Arg	Pro 335	
Lys	Asp	Gly	Thr 340	Ala	Thr	Gly	Val	Asp 345	Ala	Ile	Cys	Thr	His 350	His	Pro
Asp	Pro	Lys 355	Ser	Pro	Arg	Leu	Asp 360	Arg	Glu	Gln	Leu	Tyr 365	Trp	Glu	Leu
Ser	Gln 370	Leu	Thr	His	Asn	Ile 375	Thr	Glu	Leu	Gly	His 380	Tyr	Ala	Leu	Asp
Asn 385	Asp	Ser	Leu	Phe	Val 390	Asn	Gly	Phe	Thr	His 395	Arg	Ser	Ser	Val	Ser 400
Thr	Thr	Ser	Thr	Pro 405	Gly	Thr	Pro	Thr	Val 410	Tyr	Leu	Gly	Ala	Ser 415	Lys
Thr	Pro	Ala	Ser 420	Ile	Phe	Gly	Pro	Ser 425	Ala	Ala	Ser	His	Leu 430	Leu	Ile
Leu	Phe	Thr 435	Leu	Asn	Phe	Thr	Ile 440	Thr	Asn	Leu	Arg	Tyr 445	Glu	Glu	Asn
Met	Trp 450	Pro	Gly	Ser	_	Lys 455	Phe	Asn	Thr	Thr	Glu 460	Arg	Val	Leu	Gln
465					470					475				Leu	480
Ser	Gly	Ser	Arg	Leu 485	Thr	Leu	Leu	Arg	Pro 490	Glu	Lys	Asp	Gly	Glu 495	Ala
Thr	Gly	Val	Asp 500	Ala	Ile	Cys	Thr	His 505	Arg	Pro	Asp	Pro	Thr 510	Gly	Pro
Gly	Leu	Asp 515	Arg	Glu	Gln	Leu	Tyr 520	Leu	Glu	Leu	Ser	Gln 525	Leu	Thr	His
Ser	Ile 530	Thr	Glu	Leu	Gly	Pro 535	Tyr	Thr	Leu	Asp	Arg 540	Asp	Ser	Leu	Tyr
Val 545	Asn	Gly	Phe	Thr	His 550	Arg	Ser	Ser	Val	Pro 555	Thr	Thr	Ser	Thr	Gly 560
Val	Val	Ser	Glu	Glu 565	Pro	Phe	Thr	Leu	Asn 570		Thr	Ile	Asn	Asn 575	Leu

Arg	Tyr	Met	Ala 580	Asp	Met	Gly	Gln	Pro 585	Gly	Ser	Leu	Lys	Phe 590	Asn	Ile
	_	595			Lys		600					605			
Ser	Leu 610	Gly	Ala	Arg	Tyr	Thr 615	Gly	Cys	Arg	Val	Ile 620	Ala	Leu	Arg	Ser
625	-		_		Glu 630					635					640
				645	Pro				650					655	
			660		His			665					670		
_	_	675			Tyr		680	_	_			685			
	690				Pro	695					700				
705					Ala 710					715					720
				725	Asn			-	730		_		_	735	-
			740		Ser			745					750		
		755		_	Ser		760					765		_	
	770			_	Pro	775	_	_			780		_		=
785		_		_	His 790		_			795					800
				805	Glu				810					815	
			820		Leu			825					830		
		835			Ser Leu		840					845			
	850				Asp	855					860				
865					870 Asp				-	875					880
_				885	-			_	890	_				895	
		_	900					905	_				910		Asn
	-	915	•				920				_	925			His
	930	ı				935	i				940				Ser
945					950			_		955					960 Ser
				965	,				970	١				975	
	_	-	980)				985	•	-			990		Lys
		995	,				100	0		_		100	5		Asn
	101	.0				101	.5				102	0			Ala
102				. <u></u> 2	103				, .	103	_				1040

Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr 1045 1050 Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val 1060 1065 1070 Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn 1075 1080 1085 Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu 1090 1095 1100 Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg 1105 1110 1115 Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly 1125 1130 Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 1140 1145

<210> 480

<211> 230

<212> PRT

<213> Homo sapiens

<400> 480

Met His Arg Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu 10 Gln Thr Leu Leu Gly Pro Met Phe Lys Asn Thr Ser Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr 70 75 Asn Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu 90 Tyr Val Asn Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr 100 105 110 Pro Gly Thr Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu 120 125 Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn 135 Phe Thr Ile Thr Asn Leu Lys Tyr Glu Glu Asp Met His Cys Pro Gly 150 155 Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Ser Leu Leu Gly 165 170 Pro Met Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg 180 185 Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp 200 205 195 Ala Ile Cys Thr His Arg Leu Asp Pro Lys Ser Leu Glu Trp Thr Gly 215

<210> 481

<211> 210

<212> PRT

<213> Homo sapiens

Ser Ser Tyr Thr Gly Ser

Met Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu 5 10 Gln Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser Val Gly Pro Leu 20 25 Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Thr 40 Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro Asp Pro Lys Ser 55 60 Pro Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr 70 75 His Asn Ile Thr Glu Leu Gly Pro Tyr Ala Leu Asp Asn Asp Ser Leu 90 Phe Val Asn Gly Phe Thr His Arg Ser Ser Val Ser Thr Thr Ser Thr 105 100 110 Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser 120 125 Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu 135 Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly 150 155 Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg 170 Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg 180 185 190 Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp 200 Ala Ile 210

<210> 482

<211> 97

<212> PRT

<213> Homo sapiens

<400> 482

Met Ser Met Val Ser His Ser Gly Ala Leu Cys Pro Pro Leu Ala Phe 1 5 10 Leu Gly Pro Pro Gln Trp Thr Trp Glu His Leu Gly Leu Gln Phe Leu 30 25 Asn Leu Val Pro Arg Leu Pro Ala Leu Ser Trp Cys Tyr Ser Leu Ser 40 Thr Ser Pro Ser Pro Thr Cys Gly Met Arg Arg Thr Cys Ser Thr Leu 55 Ala Pro Gly Ser Ser Thr Pro Arg Arg Gly Ser Phe Arg Ala Cys Ser 70 75 Gly Pro Cys Ser Arg Ala Pro Val Leu Ala Leu Cys Thr Leu Ala Ala 85 90

Asp

<210> 483

<211> 438

<212> PRT

<213> Homo sapiens

<400> 483															
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	Gln	Tyr	Ser 20	Pro	Asp	Met	Gly	Lys 25		Ser	Ala	Thr	Phe		Ser
Thr	Glu	Gly 35		Leu	Gln	His	Leu 40	Leu	Arg	Pro	Leu	Phe 45	Gln	Lys	Ser
Ser	Met 50	Gly	Pro	Phe	Tyr	Leu 55	Gly	Суз	Gln	Leu	Ile 60	Ser	Leu	Arg	Pro
65	_	_	_		70					75		Суѕ			80
	_			85		_		_	90			Leu	_	95	
			100					105				Phe	110		
_	-	115					120					Gln 125			
	130	-		_		135					140	Asn			
145			-		150				_	155		Leu			160
		_	_	165					170			Gln		175	
		_	180					185				Asp	190		
		195					200					Pro 205			
	210					215					220	Phe			
225			_		230					235		Glu			240
		-		245					250			His		255	
			260					265				Lys	270		
		275					280					Glu 285			
	290			_		295			_		300	Phe			_
305					310					315		His			320
_			_	325					330			Val		335	
		-	340				_	345				Gly	350		
		355			-		360					Asp 365	_	-	
	370					375					380	Leu			
Ala 385	Val	Ile	Leu	Ile	Gly 390	Leu	Ala	Gly	Leu	Leu 395	Gly	Leu	Ile	Thr	Cys 400
		-	-	405					410	_	_	Lys	_	415	_
			420			Gln	Cys	Pro 425		Tyr	Tyr	Gln	Ser 430	His	Leu
Asp	Leu	Glu 435	Asp	Leu	Gln										

<210> 484 <211> 216

<212> PRT <213> Homo sapiens <400> 484 Met Thr Leu Lys Ser Trp Ala Pro Thr Pro Trp Thr Gly Thr Val Ser 10 Met Ser Met Val Ser Pro Ile Arg Ala Leu Cys Pro Pro Pro Ala Leu 20 25 Leu Gly Pro Pro Gln Trp Ile Ser Glu Pro Gln Trp Thr Pro Ser Ser Leu Ser Ser Pro Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe 55 Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly 70 His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly 90 Leu Leu Gly Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser 105 100 Gly Cys Arg Leu Thr Ser Leu Arg Ser Lys Lys Asp Gly Ala Ala Thr 120 125 Gly Val Asp Ala Ile Cys Ile His His Leu Asp Pro Lys Ser Pro Gly 135 140 Leu Asn Arg Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly 155 150 Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val 170 175 165 Asn Gly Phe Thr His Arg Thr Ser Val Pro Thr Thr Ser Thr Pro Gly 185 190 180 Thr Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Leu Pro 195 200 Ala Thr Gln Ser Leu Ala Leu Ser 210

<210> 485 <211> 268 <212> PRT <213> Homo sapiens

 <4400> 485

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 Thr Pro Gly Thr 10
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 Ser Gly Thr Pro Ser Ser Ser Pro 20
 Ser Pro Thr Thr Ala Gly Pro Leu 20
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 Leu Met Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu 35
 40
 45
 45

 Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr Met Glu Ser 50
 55
 60

 Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys Asn Thr Ser Val Gly 65
 70
 75
 80

 Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Lys Lys Asp 90
 95

 Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His Arg Leu Asp Pro 100
 100
 105
 110

Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu Ser Lys 120 Leu Thr Asn Asp Ile Glu Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn 135 140 Ser Leu Tyr Val Asn Gly Phe Thr His Gln Ser Ser Val Ser Thr Thr 150 155 Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Arg Thr Ser Val Asp Ser 165 170 Ile Leu Pro Leu Gln Pro His Asn Tyr Gly Cys Trp Pro Ser Pro Gly 180 185 Thr Ile His Pro Gln Leu His His His Gln Pro Ala Val Trp Gly Gly 200 His Gly Ser Pro Trp Leu Gln Glu Val Gln His His Arg Glu Gly Pro 215 220 Ala Gly Ser Ala Trp Ser His Ile Gln Glu His Gln Cys Trp Pro Ser 230 235 Val Leu Trp Leu Gln Thr Asp Leu Ser Gln Val Gln Glu Gly Trp Ser. 245 250 Ser His Trp Ser Gly Cys His Leu His Pro Ser Ser 260 265

<210> 486 <211> 304

<212> PRT

<213> Homo sapiens

<400> 486

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166

<210> 487 <211> 294 <212> PRT

<213> Homo sapiens

<400> 487 Met Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser Ser Gly Leu Thr Thr 20 25 Ser Thr Pro Trp Thr Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Pro Val Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe · 55 60 Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His 75 70 Arg Pro Gly Ser Arg Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly 90 Leu Leu Ser Pro Ile Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser 105 100 Gly Cys Arg Leu Thr Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr 120 Gly Met Asp Ala Val Cys Leu Tyr His Pro Asn Pro Lys Arg Pro Gly 135 140 Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn 150 155 Ile Thr Glu Leu Gly Pro Tyr Ser Leu Asp Arg Asp Ser Leu Tyr Val 170 175 Asn Gly Phe Thr His Gln Asn Ser Val Pro Thr Thr Ser Thr Pro Gly 185 190 . Thr Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Phe Pro Gly His Thr Glu Pro Gly Pro Leu Leu Ile Pro Phe Thr Phe Asn Phe 215 220 Thr Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser 230 235 Arg Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly Leu Leu Ser Pro 245 250 Ile Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu 260 265 270 Thr Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Met Asp Ala 275 280 Val Cys Leu Tyr Arg Pro 290

<210> 488

<211> 233

<212> PRT <213> Homo sapiens <400> 488 Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu 20 25 Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His 35 40 Phe Tyr Leu Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys 55 Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu 70 75 Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe 85 90 Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His 100 105 Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val 115 120 125 Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly 135 140 Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp 150 155 Gly Tyr Phe Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu 165 170 175 Pro Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu 180 185 Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys 195 200 205 Lys Glu Gly Glu Tyr Asn Val Gln Gln Cys Pro Gly Tyr Tyr Gln 215 Ser His Leu Asp Leu Glu Asp Leu Gln 230 <210> 489 <211> 178 <212> PRT

<213> Homo sapiens

<400> 489

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Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly 130 135 140 Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp 145 150 155 Gly Tyr Phe Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu 165 170 Pro Phe <210> 490 <211> 15 <212> PRT <213> Homo sapiens <400> 490 Thr Cys Gly Met Arg Arg Thr Cys Ser Thr Leu Ala Pro Gly Ser 1 5 10 <210> 491 <211> 15 <212> PRT <213> Homo sapiens <400> 491 Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr 10 <210> 492 <211> 15 <212> PRT <213> Homo sapiens <400> 492 Asp Gly Thr Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro 1 5 10 <210> 493 <211> 15 <212> PRT <213> Homo sapiens <400> 493 Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu 5 10 <210> 494 <211> 15 <212> PRT <213> Homo sapiens <400> 494 Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr 5 10

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Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile
                                    10
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Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu
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Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Pro Asp Glu Pro Pro Thr
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Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg
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Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly
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Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp
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Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln Gln
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Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln
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179

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<212> DNA
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<211> 185
<212> DNA
<213> Homo sapiens
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caatg
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<211> 462
<212> DNA
<213> Homo sapiens
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<213> Homo sapiens
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<213> Homo sapiens
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<211> 401
<212> DNA
<213> Homo sapiens
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ggatgccatc tgcacccacc gtcttgaccc caaaagccct ggagtggaca gggagcagct 360
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<212> DNA
<213> Homo sapiens
<400> 554
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gcagggtctg cttggtccca tgttcaagaa caccagtgtc ggccttctgt actctggctg 240
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<212> DNA
<213> Homo sapiens
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<210> 556
<211> 468
<212> DNA
<213> Homo sapiens
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<212> DNA
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<213> Homo sapiens
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<211> 468
<212> DNA
<213> Homo sapiens
<400> 559
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<212> DNA
<213> Homo sapiens
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<213> Homo sapiens .
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<212> DNA
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<212> DNA
<213> Homo sapiens
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<212> DNA
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<223> n = A, T, C or G
<400> 568
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<211> 10622
<212> DNA
<213> Homo sapiens
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      6370,7716,8210,9131,9968,10304,10363
<223> n = A, T, C or G
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190

Ala Pro Gly Ser Arg Lys Phe Asn Ala His Arg Glu Arg Thr Ala Gly 35 40 45

Ser Cys Ser Asn Pro Arg Ser Gly Ile Ala Val Trp Asn Thr Ser Ile 50 55 60

Gln Ala Ala Asp Xaa Pro His Ser Gly Gln Arg Arg Ile Ala Gln Pro 65 70 75 80

Arg Gln Trp Met Pro Ser Ala His Ile Ala Leu Thr Leu Lys Thr Ser 85 90 95

Asp Trp Thr Glu Ser Asp Cys Thr Gly Ser Xaa Ala Ile Xaa Gln Met 100 105 110

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Ser Met 130

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<222> 1,58,78,92,94

<223> Xaa = Any amino acid

<400> 572

Xaa Ile Pro Ser Ser Asn Ser Ser His Ser Pro Ile His Gly Ala Ile
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His Pro Gln Leu Gln Leu Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met 20 25 30

Arg His Leu Val Pro Gly Ser Ser Thr Arg Thr Glu Arg Glu Leu Gln 35 40 .

Gly Arg Ala Gln Thr Leu Asp Gln Glu Xaa Gln Ser Gly Ile Pro Leu 50 55 60

Phe Arg Leu Gln Thr Ser Leu Thr Gln Ala Arg Glu Gly Xaa Leu Ser 65 70 75 80

His Gly Ser Gly Cys His Leu His Thr Ser Pro Xaa Pro Xaa Arg Pro 85 90 95

Arg Thr Gly Gln Arg Ala Thr Val Leu Gly Ala Glu Gln Ser Asp Lys 100 105

Trp His Pro Gly Ala Gly Pro Leu His Pro Gly Pro Glu Gln Ser Leu 115 120 125

Cys Gln

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<210> 573

<211> 130

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<222> 1,54

<223> Xaa = Any amino acid

<400> 573

Xaa Ser Pro Ala Arg Thr Ala Ala Thr Val Pro Phe Met Val Pro Phe
5 10 15

Thr Leu Asn Phe Asn Ser Ser Pro Thr Cys Ser Thr Arg Arg Thr Cys
20 25 30

Gly Thr Trp Phe Gln Glu Val Gln Arg Ala Gln Arg Glu Asn Cys Arg
35 40 45

Val Val Leu Lys Pro Xaa Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr 50 55 60

Ser Gly Cys Arg Leu Ala Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala 65 70 75 80

Thr Ala Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Glu Asp Leu 85 90 95

Gly Leu Asp Arg Glu Arg Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn 100 105 110

Gly Ile Gln Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr 115 120 125

Val Asn 130

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<211> 156

<212> PRT

<213> Homo sapiens

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Ser Thr Val Asp Val Gly Thr Ser Gly Thr Pro Ser Ser Ser Pro Ser 20 25 30

Pro Thr Thr Ala Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg

Lys Phe Asn Thr Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr

Leu Leu Arg Pro Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Asn Asp Ile Glu Glu Leu Gly 130 135

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn

<210> 575

<211> 158

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 103

<223> Xaa = Any amino acid

<400> 575

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Pro Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn

Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly His Pro Gly

Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly

Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg

Leu Thr Ser Leu Arg Ser Xaa Lys Asp Gly Ala Ala Thr Gly Val Asp 105

Ala Ile Cys Ile His His Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg 115 120 125

Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu 130 135 140

Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 576

<211> 122

<212> PRT

<213> Homo sapiens

<400> 576

Ala Ala Gly Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr 5 10 15

Asn Leu Lys Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe 20 25 30

Asn Thr Thr Glu Arg Val Leu Gln Thr Leu Arg Gly Pro Met Phe Lys 35 40 45

Asn Thr Ser Gly Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu 50 60

Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr
65 70 75 80

His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr
85 90 95

Trp Glu Leu Ser Gln Leu Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr 100 105 110

Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 115 120

<210> 577

<211> 156

<212> PRT

<213> Homo sapiens

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<222> 11,106,151

<223> Xaa = Any amino acid

<400> 577

Gly Phe Thr His Arg Thr Ser Val Pro Thr Xaa Ser Thr Pro Gly Thr 5 10 15

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Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 150 <210> 579 <211> 155 <212> PRT <213> Homo sapiens <220> <221> variant <222> 52,138 <223> Xaa = Any amino acid <400> 579 Gly Phe Thr His Trp Ile Pro Val Pro Thr Ser Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile 35 40 Thr Asn Leu Xaa Tyr Glu Glu Asp Met His Cys Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Ser Leu Leu Gly Pro Met Phe 70 Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys 105 Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Xaa Ile Lys Glu Leu Gly Pro 135 Tyr Thr Leu Asp Ser Asn Ser Leu Tyr Val Asn 150 <210> 580 <211> 156 <212> PRT <213> Homo sapiens <220> <221> variant <222> 23 <223> Xaa = Any amino acid

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197

115 120 125

Leu Tyr Trp Gln Leu Ser Gln Met Thr Asn Gly Ile Lys Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn 145 150 155

<210> 582

<211> 156

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<213> Homo sapiens

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<222> 151

<223> Xaa = Any amino acid

<400> 582

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Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Pro Val Pro Ser 20 25 30

Pro Thr Thr Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg 50 55 60

Lys Phe Asn Ala Thr Glu Arg Val Leu Gln Gly Leu Leu Ser Pro Ile 65 70 75 80

Phe Lys Asn Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Met Asp Ala Val 100 105 110

Cys Leu Tyr His Pro Asn Pro Lys Arg Pro Gly Leu Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly 130 135 140

<210> 583

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 109,114,117,128,139 <223> Xaa = Any amino acid

<400> 583

Gly Phe Thr His Gln Asn Ser Val Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val Tyr Trp Ala Thr Thr Gly Thr Pro Ser Ser Phe Pro Gly 25 30

His Thr Glu Pro Gly Pro Leu Leu Ile Pro Phe Thr Phe Asn Phe Thr 35 40 45

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg 50 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Thr Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Gln Glu Ala Ala Thr Gly Xaa Asp Thr Ile 100 105 110

Cys Xaa His Arg Xaa Asp Pro Ile Gly Pro Gly Leu Asp Arg Glu Xaa 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Xaa Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 584

<211> 156

<212> PRT

<213> Homo sapiens

<400> 584

Gly Phe Asn Pro Trp Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr

Ser Thr Val His Leu Ala Thr Ser Gly Thr Pro Ser Ser Leu Pro Gly 25 30

His Thr Ala Pro Val Pro Leu Leu Ile Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys His Gly Ala Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr Leu Arg Leu Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr Asn Ser Val Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 585

<211> 156

<212> PRT

<213> Homo sapiens

<400> 585

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr 5 10 15

Ser Ala Val His Leu Glu Thr Ser Gly Thr Pro Ala Ser Leu Pro Gly
20 25 30

His Thr Ala Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 . 90 95

Leu Leu Arg Pro Glu Lys Arg Gly Ala Ala Thr Gly Val Asp Thr Ile 100 105 110

Cys Thr His Arg Leu Asp Pro Leu Asn Pro Gly Leu Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Lys Leu Thr Cys Gly Ile Ile Glu Leu Gly 130 135 140

Pro Tyr Leu Leu Asp Arg Gly Ser Leu Tyr Val Asn 145 150 155

<210> 586

<211>. 156

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 151,156 <223> Xaa = Any amino acid

<400> 586

Gly Phe Thr His Arg Asn Phe Val Pro Ile Thr Ser Thr Pro Gly Thr
5 10 15

Ser Thr Val His Leu Gly Thr Ser Glu Thr Pro Ser Ser Leu Pro Arg 20 25 30

Pro Ile Val Pro Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Ala Met Arg His Pro Gly Ser Arg 50 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Ile Gly Pro Leu Tyr Ser Ser Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Lys Ala Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His His Pro Asp Pro Gln Ser Pro Gly Leu Asn Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Xaa Ser Leu Tyr Val Xaa 145 150 155

<210> 587

<211> 156

<212> PRT

<213> Homo sapiens

<400> 587

Gly Phe Thr His Trp Ser Pro Ile Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Ser Ile Val Asn Leu Gly Thr Ser Gly Ile Pro Pro Ser Leu Pro Glu 20 25 30

Thr Thr Ala Thr Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asn Met Gly His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Ile Thr Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu 65 70 75 80

Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Val Ala Thr Arg Val Asp Ala Ile 100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ile Pro Gly Leu Asp Arg Gln Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly
130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 588

<211> 156

<212> PRT

<213> Homo sapiens

<400> 588

Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr
5 10 15

Phe Thr Val Gln Pro Glu Thr Ser Glu Thr Pro Ser Ser Leu Pro Gly
20 25 30

Pro Thr Ala Thr Gly Pro Val Leu Leu Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Ile Asn Leu Gln Tyr Glu Glu Asp Met His Arg Pro Gly Ser Arg

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Met Pro Leu 65 70 75 80

Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val Asp Ala Val
100 105 110

Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Arg 115 120 125

Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135

Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn 145 155

<210> 589

<211> 156

<212> PRT

<213> Homo sapiens

<400> 589

Gly Phe Thr His Gln Ser Ser Met Thr Thr Arg Thr Pro Asp Thr

Ser '	Thr	Met	His 20	Leu	Ala	Thr	Ser	Arg 25	Thr	Pro	Ala	Ser	Leu 30	Ser	Gly
?ro	Thr	Thr 35	Ala	Ser	Pro	Leu	Leu 40	Val	Leu	Phe	Thr	Ile 45	Asn	Phe	Thr
[le	Thr 50	Asn	Leu	Arg	Tyr	Glu 55	Glu	Asn	Met	His	His 60	Pro	Gly	Ser	Arg
Lys 65	Phe	Asn	Thr	Thr	Glu 70	Arg	Val	Leu	Gln	Gly 75	Leu	Leu	Arg	Pro	Val 80
Phe	Lys	Asn	Thr	Ser 85	Val	Gly	Pro	Leu	Tyr 90	Ser	Gly	Суз	Arg	Leu 95	Thr
Leu	Leu	Arg	Pro 100	Lys	Lys	Asp	Gly	Ala 105	Ala	Thr	ГЛЗ	Val	Asp 110	Ala	Ile
Cys	Thr	Tyr 115	Arg	Pro	Asp	Pro	Lys 120	Ser	Pro	Gly	Leu	Asp 125		Glu	Gln
Leu	Tyr 130	Trp	Glu	Leu	Ser	Gln 135	Leu	Thr	His	Ser	11e 140	Thr	Glu	Leu	Gly
Pro 145	Tyr	Thr	Leu	Asp	Arg 150	Asp	Ser	Leu	Tyr	Val 155	Asn				
<211 <212)> 5: L> 1: 2> P: 3> H	56	sapi	ens											
<222	l> v 2> 1			ami	no a	cid									
)> 5 Phe		Gln	Arg		Ser	· Val	Pro	Thr		Ser	Ile	Pro	Gly 15	
Pro	Thr	Val	Asp 20		Gly		Ser	Gly 25		Pro	Val	Ser	Lys		Gly
Pro	Ser	Ala 35		Ser	Pro	Lev	Leu 40		Leu	Phe	Thr	Leu 45		Phe	Thr
Ile	Thr 50		Leu	Arg	Туг	Glu 55	Glu	. Asn	Met	. Glr	His 60		Gly	Ser	Arg
Lys 65	Phe	Asn	Thr	Thr	Glu 70		y Val	Leu	Gln	Gl ₃ 75		Leu	ı Arç	g Ser	Leu 80
Phe	Lys	s Ser	Thr	Ser 85		. Gl	/ Pro	Leu	Tyr 90		: Gly	, Cys	Arq	95 95	

Leu Leu Arg Pro Glu Lys Asp Gly Thr Ala Thr Gly Val Asp Ala Ile 100 105 110

Cys Thr His His Pro Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln
115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly 130 135 140

Xaa Tyr Ala Leu Asp Asn Asp Ser Leu Phe Val Asn 145 150 155

<210> 591

<211> 155

<212> PRT

<213> Homo sapiens

<400> 591

Gly Phe Thr His Arg Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr
5 10 15

Pro Thr Val Tyr Leu Gly Ala Ser Lys Thr Pro Ala Ser Ile Phe Gly
20 25 30

Pro Ser Ala Ala Ser His Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys
50 55 60

Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe 65 70 75 80

Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu 85 90 95

Leu Arg Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys 100 105 110

Thr His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu 115 120 125

Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro 130 135 140

Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155

<210> 592

<211> 134

<212> PRT

<213> Homo sapiens

<400> 592

Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val

15 5 10 Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr 20 Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu Asp Lys 120 Asp Ser Leu Tyr Leu Asn 130 <210> 593 <211> 150 <212> PRT <213> Homo sapiens <220> <221> variant <222> 7 <223> Xaa = Any amino acid <400> 593 Gly Tyr Asn Glu Pro Gly Xaa Asp Glu Pro Pro Thr Thr Pro Lys Pro 10 Ala Thr Thr Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln 40 Tyr Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr His Pro Asp 105

Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr Trp Glu Leu Ser 120

Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr Val Leu Asp Arg

Asp Ser Leu Phe Ile Asn

<210> 594

<211> 318

<212> PRT

<213> Homo sapiens

<220>

<221> variant

<222> 136,248,268

<223> Xaa = Any amino acid

<400> 594

Gly Tyr Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn

Phe His Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser

Glu Tyr Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu

Tyr Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr

Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser

Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr

Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp 105 100

Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser

Ser Ser Thr Gln His Phe Tyr Xaa Asn Phe Thr Ile Thr Asn Leu Pro 130

Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn 155

Lys Arg Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser 170

Ile Lys Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val 185

ProAsnArg
195HisHisThrGly
200Val
200Asp
200SerLeuCys
205Asn
205PheSerProLeuAla
210Arg
210Val
215Asp
215Val
215Ala
216Ile
216Tyr
220Glu
220PheLeuArg
220MetThr
230ArgAsp
230AspPhe
230Thr
230LeuGln
230AspPhe
235Thr
235LeuAspArg
235

Ser Val Leu Val Asp Gly Tyr Xaa Pro Asn Arg Asn Glu Pro Leu Thr 245 250 255

Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Xaa Ile Gly Leu Ala 260 265 270

Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr 275 280 285

Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys 290 295 300

Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln 305 310 315

<210> 595 <211> 3451 <212> PRT <213> Homo sapiens

<220>

<221> VARIANT
<222> 177, 335, 523, 618, 663, 875, 961, 1001, 1441, 1555, 1560, 1563, 1574, 1585, 2065, 2070, 2683, 2990, 3269, 3381, 3401
<223> Xaa = Any Amino Acid

<400> 595 Ile Arg Asn Ser Ser Leu Glu Tyr Leu Tyr Ser Gly Cys Arg Leu Ala 10 1 Ser Leu Arg Pro Glu Lys Asp Ser Ser Ala Thr Ala Val Asp Ala Ile 25 Cys Thr His Arg Pro Asp Pro Glu Asp Leu Gly Leu Asp Arg Glu Arg 40 35 Leu Tyr Trp Glu Leu Ser Asn Leu Thr Asn Gly Ile Gln Glu Leu Gly 55 Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His 75 70 Arg Ser Ser Met Pro Thr Thr Ser Thr Pro Gly Thr Ser Thr Val Asp 90 Val Gly Thr Ser Gly Thr Pro Ser Ser Ser Pro Ser Pro Thr Thr Ala 110 105 100 Gly Pro Leu Leu Met Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu 125 120 115 Gln Tyr Glu Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr 140 135 130 Met Glu Ser Val Leu Gln Gly Leu Leu Lys Pro Leu Phe Lys Asn Thr 155 Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro

				165					170					175	
Xaa	Lys	Asp	Gly 180	Ala	Ala	Thr	Gly	Val 185	Asp	Ala	Ile	Cys	Thr 190	His	Arg
Leu	Asp	Pro 195	Lys	Ser	Pro	Gly	Leu 200	Asn	Arg	Glu	Gln	Leu 205	Tyr	Trp	Glu
	210					215				Leu	220				
Asp 225	Arg	Asn	Ser	Leu	Tyr 230	Val	Asn	Gly	Phe	Thr 235	His	Gln	Ser	Ser	Val 240
Ser	Thr	Thr	Ser	Thr 245	Pro	Gly	Thr	Ser	Thr 250	Val	Asp	Leu	Arg	Thr 255	Ser
			260					265		Ile			270		
		275					280			Ile		285			-
	290					295				Lys	300				
305					310					Phe 315					320
_			-	325	_	_	_		330	Ser		-		335	_
-	_		340		_		_	345		Cys -			350		_
	_	355		_			360		-	Leu	_	365			
	370					375				Pro	380				
385			-		390			-		195					400
				405				_	410	Glu		• .		415	-
			420					425		Arg			430		
		435					440			Gly		445			
	450					455				Asp	460				
465				_	470				_	Pro 475	_				480
				485		-			490	Gln				495	
			500					505		Asn			510		٠
		515		-			520			Xaa		525		_	
	530					535				Pro	540				
545	Ата	Int	Ald	сту	550	neu	neu	vaı	Leu	Phe 555	Int	ьeu	ASII	rne	560
Ile	Thr	Asn	Leu	Lys 565	Tyr	Glu	Glu	Asp	Met 570	His	Arg	Pro	Gly	Ser 575	Arg
			580			_		585		Thr			590		
		595				-	600			Ser	_	605	_		
	610	_				615	_			Thr	620		_		
Cys	Thr	His	Arg	Leu	Asp	Pro	Lys	Ser	Pro	Gly	Val	Asp	Arg	Glu	Gln

625					630					635				_	640
	-	_		645			Leu		650					655	
Pro	Tyr	Thr	Leu 660	Asp	Arg	Xaa	Ser	Leu 665	Tyr	Val	Asn	Gly	Phe 670	Thr	His
Trp	Ile	Pro 675	Val	Pro	Thr	Ser	Ser 680	Thr	Pro	Gly	Thr	Ser 685	Thr	Val	Asp
Leu	Gly 690	Ser	Glу	Thr	Pro	Ser 695	Ser	Leu	Pro	Ser	Pro 700	Thr	Thr	Ala	Gly
Pro 705		Leu	Val	Pro	Phe 710	Thr	Leu	Asn	Phe	Thr 715	Ile	Thr	Asn	Leu	Gln 720
Tyr				725			Pro		730					735	
			740				Leu	745					750		
	_	755					Cys 760					765			
	770					775					780				
785					790		Asn			795					800
				805			Lys		810					815	
_			820				Gly	825					830		
		835					Ser 840					845			
	850					855					860				
865					870		Thr			875					880
				885	1		Phe		890					895	
			900)			. Lys	905	•				910)	
		915	5				920	1				925	ı		Ala
	930)				935	5				940)			Pro
945	,	_			950)				955	i				Asn 960
				965	5				970)				975	
			980)				985	5				990)	Pro
_		99	5				100	00				100)5		Leu
	10:	10				10:	15				102	20			Asn
		r Il	e Thi	r Ası			а Туз	c Glu	ı Glu			His	s His	s Pro	Gly 1040
102 Sea	25 r Ar	д Гу	s Ph				r Gl	ı Arç				n Gly	y Lei		Gly
Pr	o Me	t Ph	_			r Se	r Vai				ту:	r Se	Gl;		Arg
Le	u Th				g Pr	o G1	u Ly:			y Ala	a Ala	a Thi	r G1		. Asp
Al	a Il	10 е Су		r Hi	s Ar	g Le			о Гу	s Sei	r Pro			u Ası	n Arg

1090				1095					1100	1			
Glu Gln Leu	Tvr	Tro				Gln	Len	Thr			Tle	Lvs	Glu
1105	-1-		1110			 .		1115		1		-1-	1120
Leu Gly Pro	Тиг	Thr			Δra	Men	Sar			V = 1	Σen	G1 v	
Ten GIA LIO	ıyı	1125		Чор	мg	ASII	1130		- y -	vas	יונשת	1135	
m				77-	D	mъ			D	G1	mL		
Thr His Arg			vaı	Ата	Pro			Inr	PIO	стХ			Int
_	1140			_	_	1145		_	_	_	1150		
Val Asp Leu 115	_	Thr	Ser	Gly	Thr 1160		Ser	Ser	Leu	Pro 1165		Pro	Thr
	_	T	T	17 1			m»	T	7			т1 ~	mb =
Thr Ala Val	Pro	ьeu	Leu			Pne	Inr	ьец			THI	TTG	THE
1170	_			1175		_	•	_	1180		_	_	
Asn Leu Gln	Tyr	GTA		_	Met	Arg	Hls			Ser	Arg	гàг	
1185		_	1190				_	1195		_	_		1200
Asn Thr Thr	Glu	_		Leu	GIn.	GTA			GIA	Pro	Leu	_	
		1205					1210					1215	
Asn Ser Ser	Val	Gly	Pro	Leu	\mathtt{Tyr}	Ser	Gly	Cys	Arg	Leu			Leu
	1220					1225					1230		
Arg Ser Glu	Lys	Asp	Gly	Ala	Ala	Thr	Gly	Val	Asp	Ala	Ile	Суз	Thr
123	5				1240)				1245	i		
His His Leu	Asn	Pro	Gln	Ser	Pro	Gly	Leu	Asp	Arg	Glu	Gln	Leu	Tyr
1250				1255	5				1260)			
Trp Gln Leu	Ser	Gln	Met	Thr	Asn	Gly	Ile	Lys	Glu	Leu	Gly	Pro	Tyr
1265			1270			-		1275			_		1280
Thr Leu Asp	Ara	Asn	Ser	Leu	Tvr	Val	Asn	Glv	Phe	Thr	His	Ara	Ser
		1285					1290					129	
Ser Gly Leu	Thr			Thr	Pro	Tro		-	Thr	Val	Asp	Leu	Glv
DOL 027 202	1300					1309					1310		4
Thr Ser Gly			Ser	Pro	Val			Pro	Thr	Thr			Pro
131		110	561	LLO			561			1325		رين	
		Dhe	Thr	T.OU	1320		ሞኮሎ	Tla	Thr			Gln	Tur
Leu Leu Val		Phe	Thr		Asn		Thr	Ile		Asn		Gln	Tyr
Leu Leu Val	Pro		•	1339	Asn 5	Phe			1340	Asn)	Leu		
Leu Leu Val 1330 Glu Glu Asp	Pro		Arg	1335 Pro	Asn 5	Phe		Lys	1340 Phe	Asn)	Leu		Glu
Leu Leu Val 1330 Glu Glu Asp 1345	Pro Met	His	Arg 1350	1339 Pro)	Asn Gly	Phe Ser	Arg	Lys 1355	1340 Phe	Asn) Asn	Leu Ala	Thr	Glu 1360
Leu Leu Val 1330 Glu Glu Asp	Pro Met	His Gly	Arg 1350 Leu	1339 Pro)	Asn Gly	Phe Ser	Arg	Lys 1355 Phe	1340 Phe	Asn) Asn	Leu Ala	Thr	Glu 1360 Val
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu	Pro Met Gln	His Gly 1365	Arg 1350 Leu	1339 Pro) Leu	Asn Gly Ser	Phe Ser Pro	Arg	Lys 1355 Phe	1340 Phe Lys	Asn) Asn Asn	Leu Ala Ser	Thr Ser 137	Glu 1360 Val
Leu Leu Val 1330 Glu Glu Asp 1345	Pro Met Gln Tyr	His Gly 1365 Ser	Arg 1350 Leu	1339 Pro) Leu	Asn Gly Ser	Phe Ser Pro Leu	Arg Ile 1370 Thr	Lys 1355 Phe	1340 Phe Lys	Asn) Asn Asn	Leu Ala Ser Pro	Thr Ser 1375 Glu	Glu 1360 Val
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu	Pro Met Gln Tyr 1380	His Gly 1365 Ser	Arg 1350 Leu Gly	1339 Pro) Leu Cys	Asn Gly Ser Arg	Phe Ser Pro Leu 1385	Arg Ile 1370 Thr	Lys 1355 Phe) Ser	1340 Phe Lys Leu	Asn) Asn Asn Arg	Leu Ala Ser Pro 1390	Thr Ser 1375 Glu	Glu 1360 Val Lys
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala	Pro Met Gln Tyr 1380 Ala	His Gly 1365 Ser	Arg 1350 Leu Gly	1339 Pro) Leu Cys	Asn Gly Ser Arg	Phe Ser Pro Leu 1385 Ala	Arg Ile 1370 Thr	Lys 1355 Phe) Ser	1340 Phe Lys Leu	Asn Asn Asn Arg	Leu Ala Ser Pro 1390 His	Thr Ser 1375 Glu	Glu 1360 Val Lys
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139	Pro Met Gln Tyr 1380 Ala	His Gly 1365 Ser) Thr	Arg 1350 Leu Gly	1339 Pro) Leu Cys Met	Asn Gly Ser Arg Asp 1400	Phe Ser Pro Leu 1385 Ala	Arg Ile 1370 Thr 5 Val	Lys 1355 Phe Ser Cys	1340 Phe Lys Leu Leu	Asn Asn Arg Tyr 140	Leu Ala Ser Pro 1390 His	Thr Ser 1379 Glu Pro	Glu 1360 Val Lys Asn
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg	Pro Met Gln Tyr 1380 Ala	His Gly 1365 Ser) Thr	Arg 1350 Leu Gly	1339 Pro Leu Cys Met	Asn Gly Ser Arg Asp 1400 Arg	Phe Ser Pro Leu 1385 Ala	Arg Ile 1370 Thr 5 Val	Lys 1355 Phe Ser Cys	1340 Phe Lys Leu Leu Tyr	Asn Asn Arg Tyr 1409	Leu Ala Ser Pro 1390 His	Thr Ser 1379 Glu Pro	Glu 1360 Val Lys Asn
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410	Pro Met Gln Tyr 1380 Ala 5 Pro	His Gly 1365 Ser Thr	Arg 1350 Leu Gly Gly	1335 Pro Leu Cys Met Asp	Asn Gly Ser Arg Asp 1400 Arg	Phe Ser Pro Leu 1385 Ala) Glu	Arg Ile 1370 Thr Val	Lys 1355 Phe) Ser Cys	1340 Phe Lys Leu Leu Tyr 1420	Asn Asn Arg Tyr 1405 Trp	Leu Ala Ser Pro 1390 His Glu	Ser 137: Glu) Pro Leu	Glu 1360 Val 5 Lys Asn Ser
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg	Pro Met Gln Tyr 1380 Ala 5 Pro	His Gly 1365 Ser Thr	Arg 1350 Leu Gly Gly	1335 Pro Leu Cys Met Asp	Asn Gly Ser Arg Asp 1400 Arg	Phe Ser Pro Leu 1385 Ala) Glu	Arg Ile 1370 Thr Val	Lys 1355 Phe) Ser Cys	1340 Phe Lys Leu Leu Tyr 1420	Asn Asn Arg Tyr 1405 Trp	Leu Ala Ser Pro 1390 His Glu	Ser 137: Glu) Pro Leu	Glu 1360 Val Lys Asn Ser
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr	Pro Met Gln Tyr 1380 Ala 5 Pro His	His Gly 1365 Ser Thr Gly	Arg 1350 Leu 5 Gly Gly Leu Ile 1430	1335 Pro Leu Cys Met Asp 1415 Thr	Asn Gly Ser Arg Asp 1400 Arg Glu	Phe Ser Pro Leu 1385 Ala) Glu Leu	Arg Ile 1370 Thr Val Gln	Lys 1355 Phe Ser Cys Leu Pro 1435	1340 Phe Lys Leu Leu Tyr 1420 Tyr	Asn Asn Arg Tyr 1409 Trp Ser	Leu Ala Ser Pro 1390 His Glu Leu	Ser 1375 Glu Pro Leu Asp	Glu 1360 Val Lys Asn Ser Arg 1440
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr	Pro Met Gln Tyr 1380 Ala 5 Pro His	His Gly 1365 Ser Thr Gly	Arg 1350 Leu 5 Gly Gly Leu Ile 1430	1335 Pro Leu Cys Met Asp 1415 Thr	Asn Gly Ser Arg Asp 1400 Arg Glu	Phe Ser Pro Leu 1385 Ala) Glu Leu	Arg Ile 1370 Thr Val Gln	Lys 1355 Phe Ser Cys Leu Pro 1435	1340 Phe Lys Leu Leu Tyr 1420 Tyr	Asn Asn Arg Tyr 1409 Trp Ser	Leu Ala Ser Pro 1390 His Glu Leu	Ser 1375 Glu Pro Leu Asp	Glu 1360 Val Lys Asn Ser Arg 1440
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr	Pro Met Gln Tyr 1380 Ala 5 Pro His	His Gly 1365 Ser Thr Gly	Arg 1350 Leu Gly Gly Leu Ile 1430 Asn	1335 Pro Leu Cys Met Asp 1415 Thr	Asn Gly Ser Arg Asp 1400 Arg Glu	Phe Ser Pro Leu 1385 Ala) Glu Leu	Arg Ile 1370 Thr Val Gln	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln	1340 Phe Lys Leu Leu Tyr 1420 Tyr	Asn Asn Arg Tyr 1409 Trp Ser	Leu Ala Ser Pro 1390 His Glu Leu	Ser 1375 Glu Pro Leu Asp	Glu 1360 Val Lys Asn Ser Arg 1440 Thr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr	Pro Met Gln Tyr 1380 Ala 5 Pro His	His Gly 1365 Ser Thr Gly Asn Val 1445	Arg 1350 Leu Gly Gly Leu Ile 1430 Asn	1335 Pro Leu Cys Met Asp 1415 Thr	Asn Gly Ser Arg Asp 1400 Arg 5 Glu	Phe Ser Pro Leu 1385 Ala) Glu Leu	Ile 1370 Thr Val Gln Gly His 1450	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn	Asn Asn Arg Tyr 1405 Trp Ser	Leu Ala Ser Pro 1390 His Glu Leu Val	Ser 137! Glu Pro Leu Asp Pro 145!	Glu 1360 Val Lys Asn Ser Arg 1440 Thr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu	Pro Met Gln Tyr 1380 Ala 5 Pro His	Gly 1365 Ser Thr Gly Asn Val 1445 Gly	Arg 1350 Leu Gly Gly Leu Ile 1430 Asn	1335 Pro Leu Cys Met Asp 1415 Thr	Asn Gly Ser Arg Asp 1400 Arg 5 Glu	Phe Ser Pro Leu 1385 Ala) Glu Leu	Arg Ile 1370 Thr Val Gln Gly His 1450	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn	Asn Asn Arg Tyr 1405 Trp Ser	Leu Ala Ser Pro 1390 His Glu Leu Val	Ser 137! Glu Pro Leu Asp Pro 145! Gly	Glu 1360 Val Lys Asn Ser Arg 1440 Thr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr	Gly 1365 Ser Thr Gly Asn Val 1445 Gly	Arg 1350 Leu 5 Gly Leu 11e 1430 Asn 5	1335 Pro Leu Cys Met Asp 1415 Thr Gly	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr	Phe Ser Pro Leu 1385 Ala Glu Leu Thr Val	Arg Ile 1370 Thr Val Gln Gly His 1450 Tyr	Lys 135! Phe Ser Cys Leu Pro 143! Gln	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn	Asn Asn Arg Tyr 1405 Trp Ser Ser	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470	Ser 137! Glu Pro Leu Asp Pro 145! Gly	Glu 1360 Val Lys Asn Ser Arg 1440 Thr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe	Gly 1365 Ser Thr Gly Asn Val 1445 Gly	Arg 1350 Leu 5 Gly Leu 11e 1430 Asn 5	1335 Pro Leu Cys Met Asp 1415 Thr Gly	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr	Phe Ser Pro Leu 1385 Ala Glu Leu Thr Val 1465 Glu	Arg Ile 1370 Thr Val Gln Gly His 1450 Tyr	Lys 135! Phe Ser Cys Leu Pro 143! Gln	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Leu	Ser 137! Glu Pro Leu Asp Pro 145! Gly	Glu 1360 Val Lys Asn Ser Arg 1440 Thr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr Pro Ser Ser	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe	His Gly 1365 Ser Thr Gly Asn Val 1445 Gly	Arg 1350 Leu 6ly Gly Leu 1430 Asn 6	1339 Pro Leu Cys Met Asp 1419 Thr Gly Ser	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr	Phe Ser Pro Leu 1385 Ala Glu Leu Thr Val 1465 Glu	Arg Ile 1370 Thr 5 Val Gln Gly His 1450 Tyr 5	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln Trp	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn Ala	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Leu	Ser 1379 Glu Pro Leu Asp Pro 1459 Gly	Glu 1360 Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr Pro Ser Ser 147 Phe Thr Phe	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe	His Gly 1365 Ser Thr Gly Asn Val 1445 Gly	Arg 1350 Leu 5 Gly Gly Leu 1430 Asn 5 Thr	1339 Pro Leu Cys Met Asp 1419 Gly Ser His	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr 1480 Thr	Phe Ser Pro Leu 1385 Ala Glu Leu Thr Val 1465 Glu	Arg Ile 1370 Thr 5 Val Gln Gly His 1450 Tyr 5	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln Trp	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn Ala	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr Leu 1485 Glu	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Leu	Ser 1379 Glu Pro Leu Asp Pro 1459 Gly	Glu 1360 Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr Pro Ser Ser 147 Phe Thr Phe 1490	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe 5 Asn	His Gly 1365 Ser Thr Gly Asn Val 1445 Gly Pro	Arg 1350 Leu 5 Gly Gly Leu 1430 Asn 5 Thr	1339 Pro Leu Cys Met Asp 1419 Gly Ser His	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr 1480 Thr	Phe Ser Pro Leu 1389 Ala Glu Leu Thr Val 1469 Glu Asn	Arg Ile 1370 Thr 5 Val Gln Gly His 1450 Tyr 5 Pro Leu	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln Trp	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn Ala Pro	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr Leu 1485 Glu	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Leu Glu	Ser 1379 Glu Pro Leu Asp Pro 1459 Gly Ile	Glu 1360 Val Lys Asn Ser Arg 1440 Thr Thr Pro
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr Pro Ser Ser 147 Phe Thr Phe 1490 Gln His Pro	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe 5 Asn	His Gly 1365 Ser Thr Gly Asn Val 1445 Gly Pro	Arg 1350 Leu 5 Gly Gly Leu 1430 Asn 5 Thr Gly Thr	1339 Pro Leu Cys Met Asp 1419 Gly Ser His Ile 1499 Lys	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr 1480 Thr	Phe Ser Pro Leu 1389 Ala Glu Leu Thr Val 1469 Glu Asn	Arg Ile 1370 Thr 5 Val Gln Gly His 1450 Tyr 5 Pro Leu	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln Trp Gly His	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn Ala Pro Tyr 1500 Glu	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr Leu 1485 Glu	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Leu Glu	Ser 1379 Glu Pro Leu Asp Pro 1459 Gly Ile	Glu 1360 Val Lys Asn Ser Arg 1440 Thr Fro Met
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr Pro Ser Ser 147 Phe Thr Phe 1490 Gln His Pro 1505	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe 5 Asn Gly	His Gly 1365 Ser Thr Gly Asn Val 1445 Gly Pro Phe Ser	Arg 1350 Leu 5 Gly Gly Leu Ile 1430 Asn 5 Thr Gly Thr	1339 Pro Leu Cys Met Asp 1419 Gly Ser His Ile 1499 Lys	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr 1480 Thr	Phe Ser Pro Leu 1385 Ala Glu Leu Thr Val 1465 Glu Asn	Arg Ile 1370 Thr Val Gln Gly His 1450 Tyr Cheu Thr	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln Trp Gly His	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn Ala Pro Tyr 1500 Glu	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr Leu 1485 Glu Arg	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Glu Val	Ser 1375 Glu Pro Leu Asp Pro 1455 Gly Ile Asn Leu	Glu 1360 Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr Pro Met
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr Pro Ser Ser 147 Phe Thr Phe 1490 Gln His Pro	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe 5 Asn Gly	His Gly 1365 Ser Thr Gly Asn Val 1445 Gly Pro Phe Ser	Arg 1350 Leu 5 Gly Gly Leu Ile 1430 Asn 5 Thr Gly Thr Arg 1510 Leu	1339 Pro Leu Cys Met Asp 1419 Gly Ser His Ile 1499 Lys	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr 1480 Thr	Phe Ser Pro Leu 1385 Ala Glu Leu Thr Val 1465 Glu Asn	Arg Ile 1370 Thr Val Gln Gly His 1450 Tyr Thr Thr	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln Trp Gly His Thr 1515 Ser	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn Ala Pro Tyr 1500 Glu	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr Leu 1485 Glu Arg	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Glu Val	Thr Ser 1375 Glu Pro Leu Asp Pro 1455 Gly Ile Asn Leu Leu	Glu 1360 Val Lys Asn Ser Arg 1440 Thr Fro Met Gln 1520 Tyr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr Pro Ser Ser 147 Phe Thr Phe 1490 Gln His Pro 1505 Gly Leu Leu	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe 5 Asn Gly Thr	His Gly 1365 Ser Thr Gly Asn Val 1445 Gly Pro Phe Ser Pro 1525	Arg 1350 Leu 5 Gly Gly Leu 1430 Asn 5 Thr Gly Thr Arg 1510 Leu	1339 Pro Pro Leu Cys Met Asp 1419 Gly Ser His Lys Phe	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr 1480 Thr 1480 Thr	Phe Ser Pro Leu 1389 Ala Glu Leu Thr Val 1469 Glu Asn Asn	Arg Ile 1370 Thr 5 Val Gln Gly His 1450 Tyr 5 Pro Leu Thr	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln Trp Gly His Thr 1515 Ser	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn Ala Pro Tyr 1500 Glu Val	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr Leu 1485 Glu Arg Gly	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Leu Glu Val Pro	Thr Ser 1375 Glu Pro Leu Asp Pro 1455 Gly Ile Asn Leu 1535	Glu 1360 Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr Pro Met Gln 1520 Tyr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr Pro Ser Ser 147 Phe Thr Phe 1490 Gln His Pro 1505	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe 5 Asn Gly Thr Arg	His Gly 1365 Ser Thr Gly Asn Val 1445 Gly Pro Phe Ser Pro 1525 Leu	Arg 1350 Leu 5 Gly Gly Leu 1430 Asn 5 Thr Gly Thr Arg 1510 Leu	1339 Pro Pro Leu Cys Met Asp 1419 Gly Ser His Lys Phe	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr 1480 Thr 1480 Thr	Phe Ser Pro Leu 1385 Ala Glu Leu Thr Val 1465 Glu Asn Asn Arg	Arg Ile 1370 Thr Val Gln Gly His 1450 Fro Leu Thr 1530 Pro	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln Trp Gly His Thr 1515 Ser	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn Ala Pro Tyr 1500 Glu Val	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr Leu 1485 Glu Arg Gly	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Glu Val Pro Glu	Ser 1375 Glu Pro Leu Asp Pro 1455 Gly Ile Asn Leu 1535 Ala	Glu 1360 Val 5 Lys Asn Ser Arg 1440 Thr 5 Thr Pro Met Gln 1520 Tyr
Leu Leu Val 1330 Glu Glu Asp 1345 Arg Val Leu Gly Pro Leu Asp Gly Ala 139 Pro Lys Arg 1410 Gln Leu Thr 1425 Xaa Ser Leu Thr Ser Thr Pro Ser Ser 147 Phe Thr Phe 1490 Gln His Pro 1505 Gly Leu Leu	Pro Met Gln Tyr 1380 Ala 5 Pro His Tyr Pro 1460 Phe 5 Asn Gly Thr Arg 1540	His Gly 1365 Ser Thr Gly Asn Val 1445 Gly Pro Phe Ser Pro 1525 Leu 0	Arg 1350 Leu 5 Gly Gly Leu 1430 Asn 5 Thr Gly Thr Arg 1510 Leu 5	1339 Pro Leu Cys Met Asp 1419 Gly Ser His Lys Phe Leu	Asn Gly Ser Arg Asp 1400 Arg Glu Phe Thr 1480 Thr Lys Leu	Phe Ser Pro Leu 1385 Ala Glu Leu Thr Val 1465 Glu Asn Asn Arg	Arg Ile 1370 Thr Val Gln Gly His 1450 Pro Leu Thr 1530 Pro 5	Lys 1355 Phe Ser Cys Leu Pro 1435 Gln Trp Gly His Thr 1515 Ser	1340 Phe Lys Leu Leu Tyr 1420 Tyr Asn Ala Pro Glu Val	Asn Asn Arg Tyr 1405 Trp Ser Ser Thr Leu 1485 Glu Arg Gly Gln	Leu Ala Ser Pro 1390 His Glu Leu Val Thr 1470 Glu Val Pro Glu 1550	Thr Ser 1375 Glu Pro Leu Asp Pro 1455 Gly Ile Asn Leu 1535 Ala	Glu 1360 Val Lys Asn Ser Arg 1440 Thr Fro Met Gln 1520 Tyr 5

		1555					1560					1565			
	1570	Asp	Arg		Xaa	Leu : 1575	Tyr '	Trp			Ser (1580				
1585	Ile	Thr			1590					1595					1600
				1605					1610		Thr '			1615	
-			1620)				1625			Thr		1630		
		1635	;				1640					1645			
	1650)				1655					Met 1660				
1665	5				1670)				1675					1680
				1685	5				1690)	Tyr			1695	
			1700)				1705	5		Ala		1710)	
		171	õ				1720)			Pro	1725)		
	173	ο.				1735	5				Asn 1740)			
Leu 174	_	Pro	Tyr	Thr	Leu 175		Arg	Asp	Ser	Leu 175	Tyr 5	Val	Asn	сту	Pne 1760
Thr	His			176	Val	Pro			177	0	Pro			1775	5 .
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	181	0 ·	_			1815	5				Gly 1820	0			
182	5				183	0				183					1840
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			186	0				186	5		Asp		187	0	
		187	5				188	0			Arg	188	5		
_	189	90				189	5				Glu 190	0			
Let 190		ı Asp	Arc	1 GTA	Ser 191		Tyr	vaı	ASI	191	Phe .5	Int	nis	ALG	1920
Phe	va:			192	Ser	Thr			193	30	Thr			193	5
			194	10				194	5		Ile		195	0	
		195	55				196	0			. Thr	196	55		
	19	70				197	5				Phe 198	0			
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Asj	ь га	s Ala	a Ala	a Thi	r Arg	y Val	Asp	Ala	9 TT	е Су	s Thr	His	H1S	rrc	Asp

			2020	`				2025					2030	١	
Pro	Gln	Ser.			Leu	Aen	Ara			T.eu	Tur	Tro			Ser
		2035	5				2040)				2045	5		
	2050)			Ile	2055	5				2060)			
Xaa 2065		Leu	Tyr	Val	Xaa 2070		Phe	Thr	His	Trp 2075		Pro	Ile	Pro	Thr 2080
		Thr	Pro	Gly 2085	Thr		Ile		Asn 2090	Leu		Thr	Ser	Gly 2095	Ile
Pro	Pro	Ser	Leu 2100	Pro	Glu	Thr	Thr		Thr		Pro	Leu	Leu 2110	Val	
Phe	Thr		Asn	-	Thr	Ile		Asn		Gln	Tyr		Glu		Met
~1		2115		_	_	_	2120					2125		_	
СТĀ	H1S		СТĀ	ser	Arg	_{- Lys} 2135		Asn	TTE	Thr	2140		vaı	тел	GIN
Gly	Leu	Leu	Lys	Pro	Leu	Phe	Lys	Ser	Thr	Ser	Val	Gly	Pro	Leu	Tyr
214					2150					2155					2160
Ser	Gly	Суз	Arg	Leu 2165	Thr	Leu	Leu	Arg	Pro 2170		Lys	Asp	Gly	Val 2175	
Thr	Arg	Val	Asp 2180		Ile	Суз	Thr	His 2189		Pro	Asp	Pro	Lys 2190		Pro
Gly	Leu	Asp 2199	-	Gln	Gln	Leu	Tyr 2200		Glu	Leu	Ser	Gln 2205		Thr	His
Ser	Ile 221		Glu	Leu	Gly	Pro 2215	_	Thr	Leu	qeA	Arg 2220		Ser	Leu	Tyr
Val			Phe	Thr	Gln			Ser	Val	Pro		-	Ser	Thr	Pro
222		,			2230	_				2235					2240
		Phe	Thr		Gln		Glu	Thr		Glu		Pro	Ser		Leu
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Pro	GLY	Pro	Thr	Ala	Thr	GTA	Pro	Val	Leu	Leu	Pro	Phe	Thr	Leu	Asn
			2260					2269	5				2270)	
Phe	Thr	Ile 2275	Ile		Leu	Gln	Tyr 2280	Glu	5				2270 Arg)	
		2275 Lys	Ile	Asn	Leu Thr		2280 Glu	Glu)	5 Glu	Asp	Met	His 2285 Gly	2270 Arg) Pro	Gly
Ser Pro	Arg 229 Leu	2275 Lys)	Ile 5 Phe	Asn Asn	Thr Thr	Thr 2299 Ser	2280 Glu 5	Glu) Arg	Glu Val	Asp Leu Leu	Met Gln 2300 Tyr	His 2285 Gly	227(Arg 5 Leu) Pro Leu	Gly Met Arg
Ser Pro 230	Arg 229 Leu 5	2275 Lys) Phe	Ile Phe Lys	Asn Asn Asn Arg	Thr Thr 2310 Pro	Thr 229! Ser	2280 Glu 5 Val	Glu) Arg Ser	Glu Val Ser Gly	Asp Leu Leu 2315 Ala	Met Gln 2300 Tyr	His 2285 Gly) Ser	2270 Arg Leu Gly	Pro Leu Cys Val	Gly Met Arg 2320 Asp
Ser Pro 2309 Leu	Arg 2290 Leu 5 Thr	2279 Lys) Phe Leu	Ile Phe Lys Leu	Asn Asn Asn Arg 2325	Thr Thr 2310 Pro	Thr 229! Ser) Glu	2280 Glu S Val Lys	Glu) Arg Ser Asp	Glu Val Ser Gly 2330 Lys	Asp Leu Leu 231! Ala	Met Gln 2300 Tyr 5 Ala	His 2285 Gly) Ser Thr	2270 Arg Leu Gly Arg	Pro Leu Cys Val 2335	Gly Met Arg 2320 Asp
Ser Pro 2309 Leu Ala	Arg 2290 Leu 5 Thr	2275 Lys) Phe Leu Cys	Ile Phe Lys Leu Thr 2340	Asn Asn Asn Arg 2325 His	Thr Thr 2310 Pro Arg	Thr 2295 Ser) Glu Pro	2280 Glu Val Lys Asp	Glu Arg Ser Asp Pro 234	Glu Val Ser Gly 2330 Lys	Leu Leu 231! Ala) Ser	Met Gln 2300 Tyr Ala Pro	His 2285 Gly Ser Thr	Arg Leu Gly Arg Leu 2350	Pro Leu Cys Val 2335 Asp	Gly Met Arg 2320 Asp Arg
Pro 2309 Leu Ala Glu	Arg 2290 Leu 5 Thr Val	Lys Phe Leu Cys Leu 235	Ile Phe Lys Leu Thr 2340 Tyr	Asn Asn Arg 2325 His Trp	Thr Thr 2310 Pro Arg	Thr 2299 Ser) Glu Pro	Z280 Glu Val Lys Asp Ser 2360	Glu Arg Ser Asp Pro 2345 Gln	Glu Val Ser Gly 2330 Lys Leu	Asp Leu 2315 Ala) Ser	Met Gln 2300 Tyr Ala Pro His	His 2285 Gly Ser Thr Gly Gly 2365	2270 Arg Leu Gly Arg Leu 2350 Ile	Pro Leu Cys Val 2335 Asp Thr	Gly Met Arg 2320 Asp Arg
Pro 2309 Leu Ala Glu	Arg 2290 Leu 5 Thr Val	Leu Cys Leu 235!	Ile Phe Lys Leu Thr 2340 Tyr	Asn Asn Arg 2325 His Trp	Thr Thr 2310 Pro Arg	Thr 2299 Ser) Glu Pro	2280 Glu Val Lys Asp Ser 2360 Arg	Glu Arg Ser Asp Pro 2345 Gln	Glu Val Ser Gly 2330 Lys Leu	Asp Leu 2315 Ala) Ser	Met Gln 2300 Tyr Ala Pro His	His 2285 Gly Ser Thr Gly Gly 2365 Val	2270 Arg Leu Gly Arg Leu 2350 Ile	Pro Leu Cys Val 2335 Asp Thr	Gly Met Arg 2320 Asp Arg
Pro 2309 Leu Ala Glu Leu Thr	Arg 2290 Leu 5 Thr Val Arg Gly 2370 His	Lys Phe Leu Cys Leu 235! Pro	Phe Lys Leu Thr 2340 Tyr	Asn Asn Arg 2325 His Trp Thr	Thr Thr 2310 Pro Arg	Thr 2299 Ser Clu Pro Leu Asp 2379 Thr	2280 Glu Val Lys Asp Ser 2360 Arg	Glu Arg Ser Asp Pro 234! Gln His	Glu Val Ser Gly 2330 Lys Leu Ser	Asp Leu 2315 Ala Ser Thr Leu	Met Gln 2300 Tyr Ala Pro His Tyr 2380 Pro	His 2285 Gly Ser Thr Gly Gly 2365 Val	2270 Arg Leu Gly Arg Leu 2350 Ile	Pro Leu Cys Val 2335 Asp Thr	Gly Met Arg 2320 Asp Arg Glu Phe
Pro 2309 Leu Ala Glu Leu Thr 2389	Arg 2290 Leu 5 Thr Val Arg Gly 2370 His	2275 Lys Phe Leu Cys Leu 2355 Pro Gln	Phe Lys Leu Thr 2340 Tyr Ser	Asn Asn Arg 2325 His Trp Thr Ser	Thr 2310 Pro Arg Lys Leu Met 2390 Ser	Thr 2299 Ser Clu Pro Leu Asp 2379 Thr	2280 Glu Val Lys Asp Ser 2360 Arg	Glu Arg Ser Asp Pro 234! Gln His	Glu Val Ser Gly 2330 Lys Leu Ser Arg	Leu Leu 2315 Ala Ser Thr Leu Thr 2395 Ser	Met Gln 2300 Tyr Ala Pro His Tyr 2380 Pro	His 2285 Gly Ser Thr Gly 2365 Val	2270 Arg Leu Gly Arg Leu 2350 Ile Asn	Pro Leu Cys Val 2335 Asp Thr Gly Ser	Gly Met Arg 2320 Asp Arg Glu Phe Thr 2400 Thr
Pro 2309 Leu Ala Glu Leu Thr 2389 Met	Arg 2290 Leu 5 Thr Val Arg Gly 2370 His 5	Leu Leu Cys Leu 2359 Pro Gln Leu	Phe Lys Leu Thr 2340 Tyr Tyr Ser Ala Pro	Asn Asn Asn Arg 2329 His Trp Thr Ser Thr 2409 Leu	Thr 2310 Pro Arg Lys Leu Met 2390 Ser	Thr 2299 Ser Glu Pro Leu Asp 2379 Thr	2280 Glu Val Lys Asp Ser 2360 Arg Thr	Glu Arg Ser Asp Pro 2349 Gln His Thr Pro	Glu Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410	Leu 2315 Ala Ser Thr Leu Thr 2395 Ser	Gln 2300 Tyr Ala Pro His Tyr 2380 Pro	His 2285 Gly Ser Thr Gly 2365 Val Asp	2270 Arg Leu Gly Arg Leu 2350 Ile Asn Thr Gly Thr	Pro Leu Cys Val 2335 Asp Thr Gly Ser Pro 2415 Ile	Gly Met Arg 2320 Asp Arg Glu Phe Thr 2400 Thr
Pro 2309 Leu Ala Glu Leu Thr 2389 Met	Arg 2296 Leu 5 Thr Val Arg 2370 His 5	Leu Cys Leu 235! Pro Gln Leu Ser Arg	Phe Lys Leu Thr 2340 Tyr Ser Ala Pro 2420 Tyr	Asn Asn Asn Arg 2329 His Trp Thr Ser Thr 2409 Leu	Thr 2310 Pro Arg Lys Leu Met 2390 Ser	Thr 2299 Ser Glu Pro Leu Asp 2379 Thr Arg	2280 Glu Val Lys Asp Ser 2360 Arg Thr Thr	Glu Arg Ser Asp Pro 2349 Gln His Thr Pro Phe 2429 His	Glu Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410	Leu Leu 2315 Ala Ser Thr Leu Thr 2395 Ser Ile	Met Gln 2300 Tyr Ala Pro His Tyr 2380 Pro Leu Asn	His 2285 Gly Ser Thr Gly 2365 Val Asp Ser Phe	2270 Arg Leu Gly Arg Leu 2350 Ile Asn Thr Gly Thr 2430 Arg	Pro Leu Cys Val 2335 Asp Thr Gly Ser Pro 2415 Ile	Gly Met Arg 2320 Asp Glu Phe Thr 2400 Thr
Pro 2309 Leu Ala Glu Leu Thr 2389 Met Thr Asn	Arg 2296 Leu 5 Thr Val Arg 2370 His 5 His Ala	Leu Cys Leu 2355 Pro Gln Leu Ser Arg 2435	Phe Lys Leu Thr 2340 Tyr Ser Ala Pro 2420 Tyr	Asn Asn Asn Arg 2329 His Trp Thr Ser Thr 2409 Glu	Thr 2310 Pro Arg Lys Leu Met 2390 Ser Leu Glu	Thr 2299 Ser Glu Pro Leu Asp 2379 Thr Arg Val	2280 Glu Val Lys Asp Ser 2360 Arg Thr Thr	Glu Arg Ser Asp Pro 2349 Gln His Thr Pro Phe 2429 His	Glu Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410 Thr	Leu 2315 Ala Ser Thr Leu Thr 2395 Ser Ile	Met Gln 2300 Tyr Ala Pro His Pro Leu Asn Gly	His 2285 Gly Ser Thr Gly 2365 Val Asp Ser Phe Ser 2445	Leu Gly Arg Leu 2350 Ile Asn Thr Gly Thr 2430 Arg	Pro Leu Cys Val 2335 Asp Thr Gly Pro 2415 Ile Lys	Gly Met Arg 2320 Asp Glu Phe Thr 2400 Thr Thr
Pro 2309 Leu Ala Glu Leu Thr 2389 Met Thr Asn	Arg 2296 Leu 5 Thr Val Arg 2370 His 5 His Ala	Leu Cys Leu 2355 Pro Gln Leu Ser Arg 2435 Thr	Phe Lys Leu Thr 2340 Tyr Ser Ala Pro 2420 Tyr	Asn Asn Asn Arg 2329 His Trp Thr Ser Thr 2409 Glu	Thr 2310 Pro Arg Lys Leu Met 2390 Ser	Thr 2299 Ser Glu Pro Leu Asp 2379 Thr Arg Val	2280 Glu Val Lys Asp Ser 2360 Arg Thr Thr Leu Met 2440 Gln	Glu Arg Ser Asp Pro 2349 Gln His Thr Pro Phe 2429 His	Glu Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410 Thr	Leu 2315 Ala Ser Thr Leu Thr 2395 Ser Ile	Met Gln 2300 Tyr Ala Pro His Pro Leu Asn Gly	His 2285 Gly Ser Thr Gly 2365 Val Asp Ser Phe Ser 2445 Pro	Leu Gly Arg Leu 2350 Ile Asn Thr Gly Thr 2430 Arg	Pro Leu Cys Val 2335 Asp Thr Gly Pro 2415 Ile Lys	Gly Met Arg 2320 Asp Glu Phe Thr 2400 Thr Thr
Pro 2309 Leu Ala Glu Leu Thr 2389 Met Thr Asn Asn	Arg 2296 Leu 5 Thr Val Arg 2370 His 5 His Ala Leu Thr 2450 Thr	Leu Cys Leu 2355 Pro Gln Leu Ser Arg 2435 Thr	Phe Lys Leu Thr 2340 Tyr Ser Ala Pro 2420 Tyr Glu	Asn Asn Asn Arg 232! His Trp Thr Ser Thr 240! Glu Arg	Thr 2310 Pro Arg Lys Leu Met 2390 Ser Leu Glu Val	Thr 2299 Ser Glu Pro Leu Asp 2379 Thr) Arg Val Asn Leu 2459 Leu	2280 Glu Val Lys Asp Ser 2360 Arg Thr Thr Leu Met 2440 Gln	Glu Arg Ser Asp Pro 2349 Gln His Thr Pro Phe 2429 His	Glu Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410 Thr His	Leu Leu 2315 Ala Ser Thr Leu Thr 2395 Ser Ile Pro Leu Cys	Met Gln 2300 Tyr Ala Pro His Pro Leu Asn Gly Arg 2460 Arg	His 2285 Gly Ser Thr Gly 2365 Val Asp Ser Phe Ser 2445 Pro	Leu Gly Arg Leu 2350 Ile Asn Thr Gly Thr 2430 Arg	Pro Leu Cys Val 2335 Asp Thr Gly Pro 2415 Ile Lys	Gly Met Arg 2320 Asp Glu Phe Thr 2400 Thr Thr Phe Lys Leu
Pro 2309 Leu Ala Glu Leu Thr 2389 Met Thr Asn Asn 2469	Arg 2296 Leu 5 Thr Val Arg 2370 His 5 His Leu Thr 2450 Thr 5	Leu Cys Leu 2355 Pro Cln Leu Ser Arg 2435 Thr	Phe Lys Leu Thr 2340 Tyr Ser Ala Pro 2420 Tyr Glu Val	Asn Asn Asn Arg 232! His Trp Thr Ser Thr 240! Glu Arg Gly	Thr 2310 Pro Arg Lys Leu Met 2390 Ser Leu Glu Val	Thr 2299 Ser Control C	2280 Glu Val Lys Asp Ser 2360 Arg Thr Thr Leu Met 2440 Gln	Glu Arg Ser Asp Pro 2349 Gln His Thr Pro Phe 2429 His Gly Ser	Glu Val Ser Gly 2330 Lys Leu Ser Arg Ala 2410 Thr His Leu Gly	Leu Leu 2319 Ala Ser Thr Leu Thr 2399 Ile Pro Leu Cys 2479	Met Gln 2300 Tyr Ala Pro His Tyr 2380 Pro Leu Asn Gly Arg 2460 Arg	His 2285 Gly Ser Thr Gly 2365 Val Asp Ser Phe Ser 2445 Pro	2270 Arg Leu Gly Arg Leu 2350 Ile Asn Thr Gly Thr 2430 Arg Val	Pro Leu Cys Val 2333 Asp Thr Gly Ser Pro 241: Ile Lys Phe Leu	Gly Met Arg 2320 Asp Arg Glu Phe Thr 2400 Thr Thr Lys Leu 2480

				2485					2490)				2495	
Ψττα	A ra	Dro	Asp			Ser	Pro				Ara	Glu	Gln	Leu	Tyr
ıyı	ьц	110	2500		,-	-		2505					2510		-
Trp	Glu	Leu 251	Ser	Gln	Leu			Ser		Thr	Glu	Leu 2525	Gly	Pro	Tyr
Thr	Leu 253	Asp	Arg	Asp	Ser	Leu 2535	Tyr	Val	Asn	Gly	Phe 2540	Thr	Gln	Arg	Ser
254	Val	Pro	Thr		2550)				2555	5				2560
Thr	Ser		Thr	2565	5				2570	0				2575)
			Leu 2580	כ				2585	5				2590)	
		259	Met 5				2600)				260	5		
	261	0	Gln			261	5				262	0			
262	5		Tyr		2630	0				263	5				2640
_	_		Ala	264	5				265	0				2655	5
			266	0				266	5				267)	
		26	r His 75				268	0				268	5		
_	269	90	ı Phe			269	5				270	0			
270	15		r Pro		271	0				271	5				2720
			r Ile	272	5				273	0				273	5
			u Asn 274	0				274	5				275	0	
		27	y Ser 55				276	0				276	55		
	27	70	g Pro			277	5				278	10			
27	85		g Leu	•	279	0				279	95				2800
				280)5				281	LO				281	
			g Glu 282	20				282	:5				283	10	
		28	u Lei 35				284	10				284	15		
	28	50				285	55				286	50			Val
		r Gl	u Gl	ı Pro			r Let	ı Asr	n Phe			e Ası	ı Ası	теи	Arg 2880
28 Ty	65 r Me	t Al	a Asj			/U y Gli	n Pro	Gl ₃				s Phe	e Asr	ılle	Thr
As	p As	n Va				s Le	u Lev				a Phe	e Glı	n Arg 29:	289 J Ser	Ser
_			29	∪∪ ~ ^	. ML-	_ (1)		290 2000		ודן.	<u>. 77</u> .	a T.e.			- Val
		29	15				292	20				29	25		Val
_	20	30	_			29	35				29	40			ı Gln
Pr	o Le	eu Se	er Gl	y Pr	o Gl	y Le	u Pro	o Ile	e Ly	s Gl	n Va	T Ph	e Hi	s Gli	ı Leu

2945	2950)		2955		29	60
Ser Gln Gln Thr	His Gly 2965	Ile Thr	Arg Leu 297		Tyr Ser	Leu Ası 2975	р
Lys Asp Ser Leu 298	-	Asn Gly	Tyr Asn 2985	Glu Pro	Gly Xaa 2990		u
Pro Pro Thr Thr 2995	_	3000	0		3005		
Glu Ala Thr Thr 3010	Ala Met	Gly Tyr 3015	His Leu	Lys Thr		Leu Ası	n
Phe Thr Ile Ser 3025	3030)		3035		30-	40
Ala Thr Phe Asn	Ser Thr 3045	Glu Gly	Val Leu 305		Leu Leu	Arg Pro	0
Leu Phe Gln Lys	0		3065		307)	
Ile Ser Leu Arg 3075		308	0		3085		
Thr Cys Thr Tyr 3090		3095		3100) '		
Gln Leu Tyr Trp 3105	3110)		3115		31	20
Gly Phe Tyr Val	3125		313	0		3135	
Pro Gln Asn Leu 314	0		3145		315	0	
Val Asn Trp Asr 3155		316	0		3165		
Thr Leu Leu Arg 3170		3175		3180	0		
Ser Gln Leu His 3185 Met Asp Ser Val	3190		_	3195		32	00
Asp Pro Ser Let	3205		321	0		3215	
322 Ser Phe His Tr	:0		3225		323	0	
3235 Thr Glu Met Glu		324	0		3245		
3250 Gln His Phe Tyr		3255		326	0		
3265 Asp Lys Ala Glr	3270)		3275		32	80
Ile Glu Asp Ala	3285		329	0		3295	
330 Tyr Phe Ser Asp	10		3305		331	0	
3315 His His Thr Gly		332	0		3325		
3330 Arg Val Asp Arg	_	3335		334	0		
3345 Asn Gly Thr Glr	3350	3		3355		33	860
Val Asp Gly Ty	3365		337	0	•	3375	
338 Asp Leu Pro Phe	10	_	3385		339	0	
3395 Gly Leu Ile Thi		340	0		3405		
	,	010	,				9

3410

Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr
3425

Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln
3445

3420

3420

3420

3420

3435

3440

3445

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<400> 596 Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Pro Gly Thr 5 10 15

Ser Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Ser Leu Pro Ser

Pro Thr Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr 35 40 45

Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met His His Pro Gly Ser Arg
50 55 60

Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu 65 70 80

Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr 85 90 95

Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile

Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln 115 120 125

Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly 130 135 140

Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn 145 150 155